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### A FURTHER REPORT ON THE PROGNOSIS OF ANGINA PECTORIS AND OF CORONARY THROMBOSIS. A STUDY OF FIVE HUNDRED CASES OF THE FORMER CONDITION AND OF TWO HUNDRED CASES OF THE LATTER\*

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SINCE the time of Heberden's classical description of angina pectoris in the eighteenth century, and doubtless for centuries before, the uncertainty of the prognosis has remained one of the outstanding features of this condition. The frequent association of angina pectoris with sudden death has made the two almost synonymous in the minds of many patients who feel that an early end is inevitable; too often such a gloomy outlook has been shared also by the physician in charge, who, perhaps with a fatalistic point of view, makes no attempt to determine the patient's chances for survival for any length of time, as for instance five years or more. But even though it is recognized that patients may live for many years after the onset of symptoms, an intelligent prognosis in the individual case still remains one of the most difficult problems in medicine. We have been very much interested in trying to find out if there are any helpful clues in this difficult task; as a result of our study we are confident that there are such clues even though there is a great deal still to learn. The tremendous importance of the subject is indicated by two facts; first, angina pectoris is one of the most common serious medical complaints today and apparently is becoming steadily more common; and second, it is particularly likely to attack people in important professional, administrative, and business positions who need to know something at least of their chances for life and work in the future.

In the present investigation we have studied a group of 500 consecutive cases of angina pectoris and 200 consecutive cases of coronary thrombosis seen in private practice during the past ten years in order to determine what the expectation of life in the two conditions

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may be, and favorable and unfavorable factors the presence of which may be of good or of ill omen for the patient. A preliminary report of the first 200 cases of angina pectoris and of 62 cases of coronary thrombosis was published five years ago.<sup>1</sup> The present paper includes a follow-up report of these cases and is in the nature of an intermediate study of the problem. After another five years or more we shall publish a more or less final report of these groups of patients.

#### PROGNOSIS IN THE PRESENT SERIES OF FIVE HUNDRED CASES OF ANGINA PECTORIS

All patients included in this series had paroxysmal oppression in the front of the chest, generally substernal, often radiating to the left arm or both arms, rarely to the right arm alone, brought on particularly by exercise, especially after eating, in cold weather, or when hurried, and relieved within a few minutes by rest or by nitrites. Many of the patients were nervous, but no attempt was made to separate "primary" from "secondary" angina pectoris; such a separation we believe is unwise, but as in the previous study, other varieties of chest or heart pain were carefully excluded from the present series of real angina pectoris.

TABLE I

#### PROGNOSIS OF ANGINA PECTORIS AND OF CORONARY THROMBOSIS

|   |  |             |
|---|--|-------------|
| <hr/>   |  |             |
| 1. <i>Angina pectoris</i> —500 cases (including follow-up of 200 cases previously reported)                               |  |             |
| 213 cases known to be dead—average duration of life after the onset of angina pectoris                                    |  | = 4.4 years |
| 273 cases known to be living—average duration of the angina pectoris  |  | = 5.1 years |
| —   |  |             |
| 486 cases—average   |  | = 4.9 years |
| 14 cases not traced   |  |             |
| Three patients had angina pectoris for over 20 years—two dead, one still alive over 21 years after onset of this trouble. |  |             |
| 2. <i>Coronary thrombosis (acute)</i> —200 cases (including follow-up of 62 cases previously reported)                    |  |             |
| 101 cases known to be dead—average duration of life after the acute cardiac infarction                                    |  | = 1.5 years |
| (range = a few hours to 11 years)   |  |             |
| 94 cases known to be alive—average duration since acute cardiac infarction  |  | = 3.2 years |
| (maximum = 17 years)  |  |             |
| —   |  |             |
| 195 cases—average   |  | = 2.4 years |
| 5 cases not traced.   |  |             |
| <hr/>   |  |             |

Of the five hundred patients with angina pectoris upon whom this study has been made, recent reports were obtained upon all except fourteen whose present status remains undetermined. Two hundred and thirteen (213) patients are dead, while two hundred and seventy-three (273) are known to be alive. Of the 213 patients known to be dead, 9 lived less than two months. In the remaining group of 204

patients the average duration from the onset of the angina pectoris to death was 4.6 years. The average duration of life in the total group of 213 cases known to be dead was 4.4 years. The average duration of the angina pectoris to date in the 273 living patients is 5.1 years, which gives an average duration of 4.9 years for the entire series of living and dead patients. In our series three patients have had angina pectoris for twenty or more years; two of these patients are dead, both having had attacks of angina pectoris for twenty years; the remaining patient is living and fairly well in spite of the fact that he has had angina pectoris for twenty-one years. Mackenzie found the average duration of life after the onset of angina pectoris to be 5.4 years in 213 patients whom he was able to follow from the onset of symptoms to death.<sup>2</sup> It seems probable that upon completion of our series the average duration of life will exceed that reported by Mackenzie and it may surpass six years.

Although the conclusions arrived at from an analysis of a large series of cases of angina pectoris cannot be applied *in toto* to the individual case, it is instructive to determine the occurrence of various factors which may influence favorably or unfavorably the course of the disease. In Table II we have presented data concerning the sex, age at onset, history or presence of hypertension or syphilis, evidence of arteriosclerosis, occurrence of coronary thrombosis clinically diagnosable, enlargement of the heart, character of the heart sounds, congestive failure, radiation of the pain to the left, right, or both arms, the severity of the pain, presence or absence of heart-block, either auriculoventricular or intraventricular, the T-wave of the electrocardiogram (in Leads I and II), the degree of nervous sensibility, and the number of cases that showed a normal heart upon physical and electrocardiographic examination. In order to give the relative frequency of the factors mentioned above, we have arranged the cases in three groupings; (1) the total series, (2) 100 patients who died within three years after the onset of angina pectoris, and (3) 100 patients who lived more than seven years after the onset.

It has been possible to determine with a fair degree of accuracy the manner or cause of death in a considerable number of the series. Of the 213 patients who died, 62 died suddenly, certainly in a large majority of cases from angina pectoris itself; in 38 other cases death was attributed definitely to coronary thrombosis; 45 more cases succumbed to congestive failure; while in 31 others death was said to be of cardiac origin but the details were insufficient to make a definite diagnosis possible. Thus, it seems evident that in the majority of the group death could be attributed directly to failure of the heart, that is, in 176 patients (82 per cent) of the 213 of the completed series. Of the remaining patients who died, various conditions were responsible, including carcinoma, pneumonia, hemiplegia,

TABLE II  
DATA OF FIVE HUNDRED CASES OF ANGINA PECTORIS

|   | TOTAL<br>500<br>PATIENTS | DEAD WITHIN<br>3 YEARS<br>(100 PATIENTS) | LIVED OVER<br>7 YEARS<br>(100 PATIENTS) |
|---|--------------------------|--|---|
| Sex:  |                          |  |   |
| Male  | 376 (75 per cent)        | 81                                       | 77                                      |
| Female  | 124 (25 per cent)        | 19                                       | 23                                      |
| Age at Onset:   |                          |  |   |
| Average   | 56.5                     | 59                                       | 53                                      |
| Limits  | 20-80                    | 24-80                                    | 20-61                                   |
| Hypertension (160/110)  | 182                      | 42                                       | 34                                      |
| Syphilis:   |                          |  |   |
| Positive  | 22                       | 6  | 3                                       |
| Questionable  | 8                        | 1  | 3                                       |
| Negative  | 470                      | 93                                       | 94                                      |
| Arteriosclerosis:   |                          |  |   |
| Positive  | 268                      | 53                                       | 45                                      |
| Questionable  | 50                       | 18                                       | 18                                      |
| Negative  | 182                      | 29                                       | 37                                      |
| Coronary thrombosis:  |                          |  |   |
| Positive  | 130                      | 34                                       | 19                                      |
| Questionable  | 75                       | 20                                       | 19                                      |
| Negative  | 295                      | 46                                       | 62                                      |
| Cardiac enlargement:  |                          |  |   |
| Positive  | 316                      | 80                                       | 55                                      |
| Questionable  | 21                       | 3  | 3                                       |
| Negative  | 163                      | 17                                       | 42                                      |
| Character of heart sounds:  |                          |  |   |
| Good  | 274                      | 44                                       | 64                                      |
| Fair  | 154                      | 34                                       | 12                                      |
| Poor  | 72                       | 22                                       | 24                                      |
| Congestive failure:   |                          |  |   |
| Positive  | 77                       | 22                                       | 13                                      |
| Negative  | 423                      | 78                                       | 87                                      |
| Pain referred to  |                          |  |   |
| Left arm alone  | 177                      | 30                                       | 45                                      |
| Right arm alone   | 20                       | 6  | 1                                       |
| Both arms   | 172                      | 38                                       | 29                                      |
| Severity of pain:   |                          |  |   |
| Uncertain   | 13                       | 4  | 1                                       |
| Mild  | 129                      | 24                                       | 26                                      |
| Moderate  | 151                      | 31                                       | 39                                      |
| Marked  | 104                      | 18                                       | 18                                      |
| Severe (decubitus)  | 103                      | 23                                       | 16                                      |
| Electrocardiogram:  |                          |  |   |
| Heart-block: auriculo-ventricular   |                          |  |   |
| Positive  | 11                       | 2  | 2                                       |
| Negative  | 382                      | 69                                       | 33                                      |
| Heart-block: intraventricular   |                          |  |   |
| Positive  | 51                       | 13                                       | 20                                      |
| Negative  | 342                      | 58                                       | 65                                      |
| Inverted T deflection<br>(Lead I or II)                                   | 58                       | 17                                       | 10                                      |
| Nervous sensibility marked  |                          |  |   |
| Positive  | 239                      | 40                                       | 52                                      |
| Negative  | 267                      | 46                                       | 31                                      |
| Normal cardiac examination,<br>blood pressure, and electro-<br>cardiogram | 74                       | 9  | 28                                      |

and postoperative complications. The average age at death for the group was 62.2 years, being slightly lower for the males (61.6 years) than for the females (64.7 years). Greater opportunity for rest in the case of women may account for this difference.

It has long been recognized that even in the presence of severe angina pectoris no abnormalities may be detectable by any method of examination. Of the group of 393 who had had electrocardiograms, 74 patients (19 per cent) showed normal hearts on physical examination (in size, sounds, rate and rhythm), normal blood pressure, and normal electrocardiograms. From Table II it will be seen that only 9 of these patients, or 12 per cent, had died in less than three years; while 28, or 37 per cent, had lived seven or more years since the onset of their symptoms, so that normal findings by the above methods of examination appear to be definitely favorable.

Fifty-eight patients of the 393 who were electrocardiographed showed an inversion of the T-wave in Leads I or II of the "coronary type," and from Table II it is seen that this occurred in 17 patients who lived less than three years after the onset of symptoms of angina pectoris, and in 10 who lived more than seven years; so that, although considered as evidence of coronary disease and usually of rather serious import, patients may live for a considerable number of years even in the presence of this definitely abnormal electrocardiographic finding.

Coronary thrombosis is a frequent complication of angina pectoris and it has been only during the last ten years that a clinical differentiation between the two conditions has been appreciated by the medical profession at large. Mackenzie included eighteen such cases in his series of 160 cases of so-called angina pectoris, nine of which were confirmed by post-mortem examination. Coronary thrombosis occurred in 130 of our total series of 500 cases (about 25 per cent). In this group of 130 patients, it occurred at the onset of the angina pectoris in 40 instances (30 per cent), and was a recognized terminal event in 33 patients (25 per cent). Two attacks of coronary thrombosis occurred in eleven of the patients. Of the 130 patients, 95 are dead (73 per cent) and the average duration of life of those followed from the onset of angina pectoris to death was 4.6 years (the same as for the group of 213 patients followed from the onset of angina pectoris to death). Of the 35 patients still alive after the complication of coronary thrombosis, 22 per cent have angina pectoris only on unusual exertion, 53 per cent have attacks precipitated by moderate exertion and their activities are considerably limited because of angina pectoris, while the remaining 25 per cent have attacks even when quiet and are in a poor condition.

Hypertension was considered to be present in those patients who had, or who had had in the past, a systolic blood pressure of 160 mm. of mercury or more, or a diastolic pressure of 110 mm. or more. There

were 182 of the total series of 500 who presented this finding, an incidence of 36 per cent. Seventy-five of the 182 patients who had hypertension are dead, the average duration of life after the onset of angina pectoris being 4 years, while the total average duration of life including the 107 hypertensive patients still living is 4.5 years. From Table II it is seen that hypertension was present more frequently in the group who succumbed within three years than in the group which survived seven years. It seems that although hypertension may not be of serious import, its presence apparently has a slightly unfavorable influence on the duration of life after the onset of angina pectoris. Our figures do not support a prevalent idea that the presence of hypertension with angina pectoris is a favorable combination.

Gallop rhythm was noted in 29 patients of whom 18 are dead; the average duration of life following the onset of angina pectoris in this latter group was only three years.

Angina pectoris decubitus is usually a sign of considerable gravity and 23 of the patients who had angina pectoris of this severity died within three years, although 16 patients lived more than seven years; thus it is possible but somewhat unusual to survive angina decubitus for many years.

A few further observations of some interest in this series of angina pectoris are to follow. From the etiological point of view, syphilis was present with certainty in only 22 patients, an incidence of 5.5 per cent. A history of rheumatic fever was given by 37 patients, but it apparently did not affect the prognosis. Evidence of arteriosclerosis by physical or by roentgen-ray examination was a frequent finding in this series, occurring in considerably more than half of the patients. The patients were divided into three groups on the basis of the quality of the heart sounds; they were considered good in 52 per cent of the cases with an average duration of life of 5.2 years for this group, fair in 32.7 per cent with an average duration of life of 4.5 years, and poor in 15.3 per cent, the duration of life after the onset of angina pectoris being 4 years. Valvular disease was found in 47 of the patients but apparently did not affect the prognosis, except in those patients who had aortic regurgitation of luetic origin, of whom there were 11 cases; eight of these 11 patients are dead with an average duration of life of 2.6 years, and three are living, the duration of life to date being 2.7 years. Alternation of the pulse was present in 15 patients, of whom 13 are dead.

The relation of angina pectoris to auricular fibrillation is of interest, since it is recognized that the two are rarely present at the same time. Of the total series, this arrhythmia was found in 19 cases. In 11 it occurred in paroxysmal form, and was a terminal event in 4 other cases. In 4 patients both angina pectoris and constant auricular fibrillation were present. Two patients had angina pectoris at the

time of their paroxysms of auricular fibrillation, an unusual and interesting combination, easily confused with acute coronary thrombosis.

One patient with arteriosclerosis and hypertension has had complete auriculoventricular block for 3.5 years with slight congestive failure at intervals and continues to have angina pectoris on exertion, but remains in fair condition.

The severity and radiation of the pain for the group are listed in Table II. Of some interest is the somewhat infrequent radiation found in 8 patients in whom the pain was referred from the substernal region to the epigastrium. In one patient the pain was first felt in the left arm and was later referred to the left chest, while in another patient a typical attack of angina pectoris on exertion began with a feeling of numbness and pain in both hands and lower arms followed shortly by radiation to the chest and upper substernal region. In 20 patients the pain was referred entirely to the right arm, and when present in the right arm the pain appears to be of more serious import than when entirely left-sided.

Attention has already been directed to one particularly favorable prognostic sign and that is the absence of all evidence of heart disease by physical examination, electrocardiography, and roentgen study. The second important favorable prognostic feature is the degree of care taken of the health. There is no doubt in the least that proper attention to the establishment of excellent habits of rest and exercise, diet, and weather, and avoidance of strain of all kinds prolongs life, sometimes for years. Exceptions always exist, but given a relatively young individual, that is under 55 years, who shows no physical evidence of heart disease and who can and will take proper care of himself or herself the prognosis may be considered as probably good for years to come in the absence of angina decubitus.

#### PROGNOSIS OF CORONARY THROMBOSIS

Although it has been only during the past decade that the clinical picture of coronary thrombosis has become familiar to physicians at large, the combination of a careful history, physical examination, and electrocardiogram often reveals evidence that such an event has occurred in the past, and it has come to be recognized as a common clinical condition. Not infrequently a patient, consulting a physician because of cardiovascular symptoms, dates the beginning of his illness to an acute episode months or even years before, which is readily recognized to have been a coronary occlusion. Much has been written on the diagnosis of coronary thrombosis, so that it is usually a relatively simple matter to make the diagnosis correctly during life providing the thrombosis occurs suddenly enough and in a vessel of sufficient calibre to produce a fair sized infarct in the myocardium, without killing the patient instantly. The prolonged terrible pain

and distress, substernal and epigastric, the failure of nitrites to relieve the pain, the need of large doses of morphine, the prostration for hours or days, and the symptoms and signs of infarction—fever, leucocytosis and sometimes pericarditis and congestive failure—the frequent history of angina pectoris, and the character of the heart sounds and the electrocardiogram, all help in establishing the diagnosis, but it is not essential to find all of these in a given case. To make a correct diagnosis in the absence of pain is more difficult; however, occasionally an acute onset of severe dyspnea (pulmonary edema), congestive failure, or of cardiac arrhythmia, supported by electrocardiographic evidence, may be sufficient to warrant a diagnosis of a painless coronary thrombosis. We have recently seen a case of this type at the Massachusetts General Hospital in which the correct diagnosis was made before death and confirmed several weeks later at post-mortem examination.

There was no clinical doubt of the diagnosis of coronary thrombosis in the two hundred patients of the present series. Two types of patients with coronary occlusion are not included in the present study; namely, (1) those cases in which the occlusion was so sudden that death occurred at once, and (2) those cases in which the occlusion occurred so slowly—by arteriosclerotic narrowing of the vessel, eventually with thrombosis—that no symptoms or signs ever developed except, perhaps, eventual congestive failure. The two groups more or less offset each other prognostically. But when the clinical diagnosis of cardiac infarction is possible, it is of great interest and of considerable importance to know what the chances of life may be. It is perhaps not adequately appreciated that acute myocardial infarction may be, and not infrequently is, compatible with many years of useful and active life, but with a life that should be lived at a somewhat lower level. In this connection a case of unusual interest is included in our series; a man of nervous temperament who had always been a strenuous worker had a classical attack of coronary thrombosis at the age of 63 years, which attack was followed by rest in bed and a prolonged convalescence of several months. Two years later he passed a life insurance examination easily, and nine years later (aged 72) he climbed Mt. Moosilauke in New Hampshire nine times in the course of a year without difficulty. At the present time he is living at the age of 79 years and leads a fairly active life for a man of his age, walking five miles a day, but he has occasional substernal oppression on undue exertion when he forgets himself.

Conner and Holt<sup>3</sup> have recently published an interesting study of the records of 287 cases of coronary thrombosis. They have summarized their findings as follows: "Approximately 85 per cent of these cases were found in men and 15 per cent in women.

"An analysis of the age incidence at the time of the first attack discloses the fact that in one-third of all the cases the first attack occurred before the fifty-first year, and in three-fourths of the cases before the sixty-first year. It seems evident therefore that coronary thrombosis must be regarded as essentially a disease of early middle life rather than of elderly life as it is usually held to be.

"Evidence of an antecedent arterial hypertension was found in 34 per cent of the cases, of syphilis in 14 per cent, and of diabetes in 10 per cent.

"Of the 287 patients studied 117 are known to be living and 142 to have died.

"The immediate mortality in the first attack was 16.2 per cent.

"Of 117 patients who recovered satisfactorily from the first attack, 75 per cent were in good health at the end of one year; 56 per cent at the end of two years; 21 per cent at five years, and 3.4 per cent at ten years. One patient remained in good health for seventeen years and died in a second attack eighteen years after the first.

"In 62 per cent of the patients the first attack supervened, without antecedent circulatory symptoms, in persons who had no reason to doubt the integrity of the heart.

"A single attack only of thrombosis is recorded in 67 per cent of all the patients; two attacks occurred in 24 per cent; three attacks in 4 per cent; and from four to seven attacks in 5 per cent.

"Of the patients having but a single attack, one-half are living and one-third are in good health.

"Among the patients having two or more attacks the time interval between the first and the second attack was less than one year in half the cases and in the other half varied from one to eighteen years.

"Signs of arterial embolism appeared 49 times among 42 patients. Twenty-eight of the embolic attacks involved the systemic arteries and 21 the pulmonary artery.

"Although the immediate mortality in attacks of coronary thrombosis is higher when the initial symptoms are severe than when they are mild, yet almost one-third of the patients who recovered from the attack had symptoms of very severe character."

Levine<sup>4</sup> has published a review of 145 cases in the course of a general survey of coronary thrombosis. As to prognosis he writes:

"There are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis. . . .

"A patient may seem to have had a mild attack and be progressing most satisfactorily, having no complaints and showing nothing remarkable on examination, and then die suddenly on the fifth to seventh day after the attack. The reverse is true, namely that after a very violent attack with serious complication, recovery can take



place. For this reason the prognosis in all cases must be guarded until a few weeks have elapsed, and contrariwise, hope should be held out and every effort in the way of treatment should be carried out in the face of apparently desperate circumstances. . . .

"The factor of age is of some importance in the prognosis as far as immediate recovery is concerned. The average age of those who recovered was 54.7 years, of those who died 61.0 years, and of the entire group 57.8 years. This would indicate that the younger are a little more apt to recover. It is also true that having recovered from the attack, the younger are more apt to continue in good health for a longer time. . . .

"The criteria for prognosis in individual cases were found to be most unsatisfactory. In general about 50 per cent have an immediate recovery. No single feature seemed to be reliable as indicative of a good or poor prognosis. Apparently mild cases occasionally died and very severe ones recovered. Slight differences in the mortality were found when certain factors were analyzed such as age, sex, the development of pericarditis, and auricular fibrillation. Ventricular tachycardia and heart-block seemed to have a greater mortality than the average. Even the type of change in the electrocardiogram had no influence on whether the patient would recover or not."

#### PRESENT SERIES OF TWO HUNDRED CASES OF CORONARY THROMBOSIS

The present series of two hundred cases includes 125 patients with angina pectoris who had coronary thrombosis also, and in addition there were 75 more patients who did not have angina pectoris. The cases have been tabulated, like the cases of angina pectoris, in three groups: (1) total series; (2) thirty-three who, although surviving the acute attack by at least one month, died in less than one year after the attack of coronary thrombosis, and (3) thirty-three who have survived by four years or more the acute attack.

Of the total series of 200 patients (Table I), five have not been heard from recently, and since three of these were in a poor condition when last heard from several years ago, it is probable that these patients are dead. One hundred and one patients (50.5 per cent) are known to be dead, of whom all died cardiac deaths except six, and of these six patients the cause of death could not be determined with any degree of certainty in four, one died of carcinoma, and the remaining patient committed suicide. From this data it will be seen that even though the patient survives the first attack of coronary thrombosis for months or years, he almost invariably succumbs eventually to cardiac failure, either congestive heart failure, angina pectoris, or a subsequent coronary occlusion. It is of interest to compare these findings with those in the series of patients with angina pectoris in which 82 per cent of the completed series of 213 patients

died cardiac deaths. More than one attack of coronary thrombosis is not unusual. Twenty patients of this series survived two attacks, eight patients survived three, and another patient had three definite attacks in the course of several years, but finally succumbed to the fourth.

The average duration of life after the first attack of coronary thrombosis for the 101 patients who died was 1.5 years—ranging from a few hours to eleven years. If we exclude the 21 patients who did not survive the acute attack by one month, the average duration of life of the remaining 80 patients was 1.9 years. The average duration of life after the attack of coronary thrombosis in the 94 patients known to be still alive is 3.2 years, giving an average of 2.4 years for the entire, but uncompleted, series of 200 cases. This figure will be lengthened considerably upon completion of the series when a final report will be made. The longest duration of life following an attack of coronary thrombosis in our series has been 17 years and occurred in a minister who has had two subsequent attacks but at the present time remains in relatively good health at 64 years of age with, however, occasionally substernal oppression on exertion. It has been pointed out before that many of the patients who had the combination of angina pectoris and coronary thrombosis were included in both series. In the preceding study of angina pectoris the complication of coronary thrombosis was found not to have affected appreciably the prognosis. From Table III it is seen that angina pectoris complicated coronary thrombosis an equal number of times (23) in the group which succumbed within one year and in the group which survived four years.

Hypertension was considered present, as in the angina pectoris series, in those patients who had at the time of examination, or who gave a history of having had in the past, a blood pressure of 160 or more mm. of mercury systolic or of 110 or more mm. diastolic. There were fifty patients who presented this finding, and of this group thirty are dead with an average duration of life following coronary thrombosis of 2.4 years, while the remaining twenty who are still alive have had an average duration of life to date of 2.4 years also, which happens to be the same as that of the entire series of 200 cases. It is seen in Table III that hypertension was noted only slightly more frequently in those who died within one year than in those who survived four years. From the data presented it seems that the presence of hypertension in this group of fifty patients has not affected the ultimate prognosis.

Cardiac enlargement occurred twenty-six times in the thirty-three patients who died within one year, and seventeen times in the same number who survived four years. As in the case of the angina pec-

TABLE III  
DATA OF TWO HUNDRED CASES OF CORONARY THROMBOSIS

|   | TOTAL<br>(200 PATIENTS) | DEAD AFTER<br>1 MONTH AND<br>WITHIN 1 YEAR<br>(33 PATIENTS) | LIVED OVER<br>4 YEARS<br>(33 PATIENTS) |
|---|-------------------------|---|--|
| Sex:  |                         |   |  |
| Male  | 167 (83.5 per cent)     | 27  | 23                                     |
| Female  | 33 (16.5 per cent)      | 6   | 10                                     |
| Age at Onset:   |                         |   |  |
| Average   | 56.7                    | 58  | 55                                     |
| Limits  | 26-80                   | 37-75   | 39-71                                  |
| Angina Pectoris:  |                         |   |  |
| Total   | 125                     | 23  | 23                                     |
| Interval between onset and<br>coronary thrombosis       |                         |   |  |
| 0-1 year*   | 73                      | 10  | 15                                     |
| 1-2 years   | 9                       | 0   | 0                                      |
| 2-5 years   | 29                      | 9   | 5                                      |
| More than 5 years                                       | 14                      | 4   | 3                                      |
| Hypertension (160/110)                                  | 50                      | 9   | 7                                      |
| Syphilis:   |                         |   |  |
| Positive  | 7                       | 1   | 0                                      |
| Questionable  | 1                       | 1   | 0                                      |
| Negative  | 192                     | 31  | 15                                     |
| Cardiac Enlargement:                                    |                         |   |  |
| Positive  | 148                     | 26  | 17                                     |
| Negative  | 52                      | 7   | 16                                     |
| Congestive Failure:                                     |                         |   |  |
| Positive  | 67                      | 18  | 5                                      |
| Negative  | 133                     | 15  | 28                                     |
| Character of heart sounds:                              |                         |   |  |
| Good  | 71                      | 5   | 11                                     |
| Fair  | 69                      | 11  | 11                                     |
| Poor  | 70                      | 17  | 11                                     |
| Pericarditis diagnosed clinically<br>at time of attack: |                         |   |  |
| Positive  | 20                      | 7   | 0                                      |
| Negative  | 147                     | 20  | 20                                     |
| Questionable  | 33                      | 6   | 13                                     |
| Paroxysmal fibrillation at time<br>of attack:           |                         |   |  |
| Positive  | 13                      | 4   | 5                                      |
| Negative  | 176                     | 28  | 28                                     |
| Questionable  | 11                      | 1   | 0                                      |
| Prolonged fever at time of<br>attack                    | 85                      | 13  | 11                                     |
| Electrocardiogram:                                      |                         |   |  |
| Auriculoventricular block                               |                         |   |  |
| Positive  | 11                      | 3   | 1                                      |
| Negative  | 116                     | 12  | 26                                     |
| Intraventricular block                                  |                         |   |  |
| Positive  | 31                      | 3   | 11                                     |
| Negative  | 96                      | 12  | 16                                     |
| Abnormal T-waves<br>(Lead I or II)                      |                         |   |  |
| Condition at last report                                |                         |   |  |
| Good  | 68                      | 0   | 20                                     |
| Fair  | 17                      | 0   | 4                                      |
| Poor  | 14                      | 0   | 2                                      |
| Dead  | 101                     | 33  | 7                                      |

\*Included in this group are twenty-five patients whose angina pectoris began at the same time as the coronary thrombosis and five patients who had angina pectoris at varying intervals after the coronary thrombosis.

toris series, syphilis was rarely present. Congestive failure was noted in sixty-seven patients and appears to add considerably to the gravity of the prognosis. Forty-six of the patients with this finding are dead and twenty-one are living; it occurred more than three times as often in the group that lived less than a year than in those who survived four years.

A considerable number of this series were not seen by the authors at the time of the acute attack, so that the relative number of those listed as having a pericardial friction rub at that time is undoubtedly much less than their actual occurrence. Pericarditis was noted more frequently in those who died early, while prolonged fever was present only slightly more often in the group that died within one year than in the group that survived four years. The electrocardiogram did not help in determining the gravity of the prognosis. Auriculoventricular block was slightly more frequent in the patients who died early, but intraventricular block as well as an abnormality, usually an inversion, of the T-wave in Leads I or II of the "coronary" type were encountered more often in those who survived. The treatment, consisting primarily of rest with long convalescence and a careful life afterward, was generally much better carried out in the patients who survived than in those who died.

#### SUMMARY AND CONCLUSIONS

1. A clinical study has been made of five hundred cases of angina pectoris and of two hundred cases of coronary thrombosis. An analysis is presented of certain factors the presence of which may or may not influence the gravity of the prognosis. The importance of the subject is evident because of the increasing frequency of angina pectoris and of the responsible position in the community of many of the patients.

2. Prognosis of Angina Pectoris. Of the series of five hundred patients with angina pectoris two hundred and thirteen are dead with an average duration of life of 4.4 years after the onset of the disease. The average duration of life to date for the total series of five hundred cases is 4.9 years. Of the patients who died death could be attributed to failure of the heart in 82 per cent, and a sudden exitus was frequently encountered. About one-fifth (19 per cent) had normal hearts on physical examination, normal blood pressures, and normal electrocardiograms. This combination of findings was an unusually favorable sign. Coronary thrombosis, although frequently encountered, did not affect appreciably the duration of life, provided the patient survived the acute attack. The presence of hypertension appeared not to be of serious import. The electrocardiogram was of little help in predicting the outcome, although a "coronary" type of T-wave in Lead I or II was seen more often in the patients who died

early. The presence of syphilis, angina decubitus, poor heart sounds, definite cardiac enlargement, congestive failure, or marked arteriosclerosis appears to be unfavorable, and the more of these factors present in the given case, the worse is the prognosis. A vital factor in the prognosis is the degree of care to which the patient can and will submit; the more careful the life of the individual, the longer as a rule will he live.

3. Prognosis of Coronary Thrombosis. Patients often survive coronary thrombosis for many years in good or fair condition. Of the series of two hundred patients with this condition, one hundred and one are dead with an average duration of life following the attack of 1.5 years. The average duration to date for the entire series of two hundred patients is 2.4 years. The patients who died almost invariably succumbed to failure of the heart. The younger patients as a rule lived a little longer; the sex appeared to be unimportant. Neither the previous occurrence of angina pectoris nor its duration prior to the attack of coronary thrombosis has seemed to matter. Hypertension was not important. Syphilis was rarely encountered. Cardiac enlargement of considerable degree is a somewhat unfavorable sign, while the presence of congestive failure and poor heart sounds adds considerably to the gravity of the prognosis. The electrocardiogram did not help appreciably in this series. Good treatment was important.

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# THE ELECTROCARDIOGRAM IN LUETIC, ARTERIOSCLEROTIC, AND RHEUMATIC HEART DISEASE\*

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THE purpose of this study was to ascertain what electrocardiographic changes would be found in a series of cases of advanced luetic heart disease. In order to have a basis of comparison, it was decided to include like numbers of cases of luetic, arteriosclerotic and rheumatic heart disease. One hundred cases of each group were therefore analyzed. No effort was made to select the cases. The electrocardiographic record book of the Cincinnati General Hospital was taken, and 100 consecutive cases of each group were set down. Thereupon the clinical case histories were gone over, so that the diagnosis could be verified. Cases in which the diagnosis was in doubt were excluded, and next consecutive verified cases were substituted. The cardiovascular material at the Cincinnati General Hospital happens to be very large, so that in going over the records for two and one half years, the 300 cases were obtained without difficulty. All cases showing improvement or remaining unchanged were followed for a period of at least six months. In this study no reference is made to the symptoms and signs presented by the patients. Emphasis is laid chiefly upon the electrocardiographic findings and mortality statistics. It was felt that a comparison of the findings in luetic, arteriosclerotic and rheumatic heart disease would be of value. Analysis of the autopsy findings is reserved for future study. Summaries of the various analyses are herewith presented, with comment.

*Sex, Color and Age Groups and General Mortality.*—In the luetic group there were 38 deaths. The average age of all the patients was 48.49 years. There were 81 males (63 colored), 19 females. In the arteriosclerotic group there were 28 deaths. The average age was 59.59 years. There were 65 males, 35 females. In the rheumatic group there were 14 deaths. The average age was 30.08 years. There were 56 males, 44 females.

In the luetic group 66 per cent of the cases occurred between the ages of 40 and 59 years. In the arteriosclerotic group 68 per cent of the cases occurred between the ages of 50 and 79 years. In the rheumatic group 70 per cent of the cases occurred between the ages of 10 and 39 years.

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*Arrhythmias.*—In the luetic group 54 of the 100 cases showed some form of arrhythmia. Of these, 23 died (42.5 per cent). In the arteriosclerotic group 35 of the 100 showed arrhythmia. Of these, 13 died (37.1 per cent). In the rheumatic group 33 of the 100 showed arrhythmia. Of these, 8 died (24.2 per cent). Abnormal T-waves were found in a large proportion of the fatal cases in all groups, in addition to premature contractions. In the luetic group the specific mortality for the cases showing some form of heart-block was approximately 50 per cent. Slightly higher mortality figures for heart-block were found in the arteriosclerotic group. In the rheumatic group the specific mortality was slightly lower.

*Fibrillation.*—A special study of the incidence of auricular fibrillation in the 300 cases was made. In the luetic group, there were 10 cases, all males; with an average age of 55.6 years. Of these, 4 died (40 per cent). Of the 10 cases, 3 had aortic insufficiency, and 7 had luetic aortitis without insufficiency. All of the deaths (4) occurred in cases of aortitis without insufficiency. The diagnosis was confirmed in each instance at autopsy. These findings are at variance with those of Juster and Pardee,<sup>1</sup> who found fibrillation only in the luetic cases with aortic insufficiency. In the arteriosclerotic group 15 cases (9 males, 6 females) showed fibrillation. The average age was 65 years. Of these, 3 died (20 per cent). In the rheumatic group 18 cases (11 males, 7 females) showed fibrillation. The average age was 43.8 years. Of these, 3 died (16.6 per cent).

*Axis Deviation.*—In the luetic group 47 cases showed left axis deviation. Twenty-seven of these occurred in patients with aortic insufficiency. Of these, 13 died. Twenty occurred in patients with aortitis without insufficiency. Of these, 7 died. In the arteriosclerotic group 29 cases showed left axis deviation. Of these, 9 died. One case showed right axis deviation. Condition remained unchanged. In the rheumatic group there were 7 instances of left axis deviation. None of these died. There were 9 instances of right axis deviation, with one death.

The incidence of left axis deviation in this series was not as high as in some other series reported. Thus Master<sup>2</sup> found left axis deviation the most common electrocardiographic abnormality in a series of 152 cases of hypertensive heart disease (74 per cent). His second most common finding was a combination of left axis deviation with inversion of T in Lead I. These cases showed a mortality in his series of 27 per cent, while his general mortality was 18 per cent. In the series here reported, this combination occurred seven times in the luetic group. (Mortality 28.5 per cent. General mortality for the group 38 per cent). In the arteriosclerotic group, the combination occurred six times. (Mortality 33 per cent. General group mortality 28 per cent.) Ziskin,<sup>3</sup> in a series of 100 consecutive patients

with hypertension, found left axis deviation in only 44 cases. He made no study of the combination of left axis deviation and inversion of T in Lead I.

In both the luetic and arteriosclerotic groups of the series here reported, the specific mortality for all cases showing left axis deviation was slightly above the general mortality figure, but the difference was not striking.

*Lengthened P-R Interval and Heart-Block.*—In the luetic group 15 cases showed lengthened P-R interval. Seven of these patients died, showing a specific mortality for lengthened P-R of 46.6 per cent. Fourteen of the luetic cases showed some form of heart-block. Seven of these died, showing a specific mortality for heart-block of 50 per cent. The gross mortality for the luetic group was 38 per cent. In the arteriosclerotic group, 6 cases showed lengthened P-R. (One death. Specific mortality 16.6 per cent.) Five cases showed some form of heart-block. (Four deaths. Specific mortality 80 per cent.) The gross mortality for the arteriosclerotic group was 28 per cent. In the rheumatic group, 12 cases showed lengthened P-R. (Two of these died. Specific mortality 16.6 per cent.) Eight cases showed some form of heart-block. (Three deaths. Specific mortality 37.5 per cent.) The gross mortality for the rheumatic group was 14 per cent.

*Abnormal QRS Complex.*—Analysis was made on the basis of finding (a) low voltage in all leads, (b) notching or slurring of the complex, and (c) notching and widening of QRS (over 0.12").

With reference to low voltage the figures for all groups were: luetic group 14 cases, 8 deaths (specific mortality 57.1 per cent); arteriosclerotic 13 cases, 5 deaths (specific mortality 38.4 per cent); rheumatic group 11 cases, 2 deaths (specific mortality 18.1 per cent). Hepburn and Jamieson<sup>4</sup> say that low voltage, even though unaccompanied by other electrocardiographic abnormalities is a prognostic sign of serious import. Willius and Killins<sup>5</sup> as the result of their study of a series of cases do not feel that this is a justifiable statement. The subject is still under discussion. In the series here analyzed it is noteworthy that the low voltage cases in the luetic group had a mortality far above the average. In the arteriosclerotic group the excess mortality for low voltage was not nearly so great, while in the rheumatic group it was hardly noticeable. Analysis with reference to notching or slurring of the QRS complex showed no marked increase in the specific mortality in any of the groups. Heimann<sup>6</sup> studied a series of 85 cases of cardiovascular syphilis and referred to a notching of QRS which he found in 30 per cent of these cases. Juster and Pardee in their series of 50 cases of luetic heart disease<sup>1</sup> found only 7 cases showing the notch of Heimann's illustration. (The notch is not accurately described.) In this series of 100 cases, such notching was found only 9 times. Notching and widening of the QRS



TABLE I  
ABNORMAL T-WAVE—ALL GROUPS

|                        | LUNG HEART DISEASE<br>100 CASES |          |            | ARTERIOSCLEROTIC HEART DISEASE<br>100 CASES |          |            | RHEUMATIC HEART DISEASE<br>100 CASES |          |           |
|------------------------|---------------------------------|----------|------------|---|----------|------------|--------------------------------------|----------|-----------|
|                        | DIED                            | IMPROVED | UNCHANGED  | DIED  | IMPROVED | UNCHANGED  | DIED                                 | IMPROVED | UNCHANGED |
| Inverted I             | 2                               | 6        | 0          | 4   | 5        | 0          | 1                                    | 1        | 0         |
| Inverted II            | 1                               | 0        | 0          | 0   | 1        | 0          | 0                                    | 1        | 0         |
| Inverted I and II      | 2                               | 4        | 1          | 0   | 6        | 2          | 0                                    | 1        | 0         |
| Inverted II and III    | 1                               | 2        | 0          | 0   | 3        | 0          | 0                                    | 4        | 0         |
| Inverted all           | 0                               | 2        | 0          | 3   | 4        | 1          | 2                                    | 0        | 0         |
| Diphasic I             | 1                               | 1        | 0          | 0   | 3        | 1          | 0                                    | 0        | 0         |
| Diphasic II            | 0                               | 0        | 0          | 1   | 0        | 0          | 0                                    | 0        | 0         |
| Diphasic I and II      | 2                               | 3        | 0          | 0   | 1        | 0          | 0                                    | 2        | 0         |
| Isoelectric            | 1                               | 7        | 1          | 0   | 7        | 0          | 1                                    | 3        | 0         |
| Low Voltage            | 2                               | 2        | 0          | 1   | 1        | 0          | 0                                    | 2        | 0         |
| Coronary I             | 6                               | 9        | 2          | 3   | 2        | 3          | 2                                    | 4        | 1         |
| Abnormal S-T Seg.      | 6                               | 5        | 1          | 2   | 9        | 5          | 0                                    | 2        | 2         |
| Coronary T             |                                 |          | 17 cases   | Coronary T                                  |          | 8 cases    | Coronary T                           |          | 7 cases   |
| Abnormal S-T Seg.      |                                 |          | 12 cases   | Abnormal S-T Seg.                           |          | 16 cases   | Abnormal S-T Seg.                    |          | 4 cases   |
| All other abnormal T   |                                 |          | 41 cases   | All other abnormal T                        |          | 44 cases   | All other abnormal T                 |          | 18 cases  |
| Total abnormal T       |                                 |          | 70 cases   | Total abnormal T                            |          | 68 cases   | Total abnormal T                     |          | 29 cases  |
| Incidence Coronary T   |                                 |          | 17 (24.3%) | Incidence Coronary T                        |          | 8 (11.7%)  | Incidence Coronary T                 |          | 7 (24.1%) |
| Incidence abnormal S-T |                                 |          | 12 (17.1%) | Incidence abnormal S-T                      |          | 16 (23.5%) | Incidence abnormal S-T               |          | 4 (13.7%) |

was associated with a specific mortality above the average in each group of this series. This same statement holds good for all three forms of abnormal QRS, considered as an entity in each group.

*Abnormal T-wave.*—The high incidence of abnormal T-wave in both the luetic and arteriosclerotic groups is in consonance with the findings of many observers. Details of the analysis are shown in the tables. (Tables I and II.)

Attention may be called to the fact that the specific mortality for abnormal T-waves (all forms) is higher in the luetic than in the arteriosclerotic group. So far as the "coronary T-wave" is concerned, the mortality in the luetic group was almost twice that in the arterio-

TABLE II  
ABNORMAL T-WAVE—ALL CASES. INCIDENCE AND MORTALITY

| LUETIC HEART DISEASE<br>100 CASES   |    | ARTERIOSCLEROTIC HEART<br>DISEASE 100 CASES   |    | RHEUMATIC HEART DISEASE<br>100 CASES   |    |
|---|----|---|----|--|----|
| Gross Mortality 38%   |    | Gross Mortality 28%   |    | Gross Mortality 14%  |    |
| Cases showing abnormal<br>T-wave (including Cor-<br>onary T) 70                       |    | Cases showing abnormal<br>T-wave (including<br>Coronary T) 68                         |    | Cases showing abnormal<br>T-wave (including Cor-<br>onary T) 29                      |    |
| Died  | 24 | Died  | 14 | Died   | 6  |
| Aortic Insufficiency  | 16 |   |    |  |    |
| Aortitis  | 8  |   |    |  |    |
| Improved  | 41 | Improved  | 42 | Improved   | 20 |
| Aortic Insufficiency  | 23 |   |    |  |    |
| Aortitis  | 18 |   |    |  |    |
| Unchanged   | 5  | Unchanged   | 12 | Unchanged  | 3  |
| Aortic Insufficiency  | 1  |   |    |  |    |
| Aortitis  | 4  |   |    |  |    |
| Specific Mortality for ab-<br>normal T-wave (includ-<br>ing Coronary T) 24<br>(34.2%) |    | Specific Mortality for ab-<br>normal T-wave (in-<br>cluding Coronary T)<br>14 (20.5%) |    | Specific Mortality for ab-<br>normal T-wave (includ-<br>ing Coronary T) 6<br>(20.6%) |    |
| Coronary T-wave (includ-<br>ing abnormal S-T Seg.)<br>No. of cases 29                 |    | Coronary T-wave (includ-<br>ing abnormal S-T<br>Seg.)<br>No. of cases 24              |    | Coronary T-wave (includ-<br>ing abnormal S-T Seg.)<br>No. of cases 11                |    |
| Died  | 12 | Died  | 5  | Died   | 2  |
| Aortic Insufficiency  | 7  |   |    |  |    |
| Aortitis  | 5  |   |    |  |    |
| Improved  | 14 | Improved  | 11 | Improved   | 6  |
| Aortic Insufficiency  | 9  |   |    |  |    |
| Aortitis  | 5  |   |    |  |    |
| Unchanged   | 3  | Unchanged   | 8  | Unchanged  | 3  |
| Aortic Insufficiency  | 0  |   |    |  |    |
| Aortitis  | 3  |   |    |  |    |
| Specific Mortality for Cor-<br>onary T-wave 12<br>(41.3%)                             |    | Specific Mortality for<br>Coronary T-wave 5<br>(20.8%)                                |    | Specific Mortality for Cor-<br>onary T-wave 2 (18.1%)                                |    |

sclerotic group. Naturally the "coronary T-wave" mortality was lowest in the rheumatic group. Juster and Pardee<sup>1</sup> found the abnormal T-wave in 85 per cent of their 50 luetic cases. The incidence of abnormal T was much higher in their cases of aortitis without valvular lesion. In this series of 100 luetic cases there was an abnormal T-wave in 70 per cent. Analysis of the two groups of luetic cases, simple aortitis, and aortitis with insufficiency, showed that the valvular group had a higher incidence of abnormal T, a higher incidence of "Coronary" T, but the discrepancy as noted by Juster and Pardee was not so marked.

A comparison of all electrocardiographic changes in the two types of luetic lesion showed no findings characteristic for either group.

*Normal Electrocardiograms.*—In the luetic group there were six normal electrocardiograms, with one death; in the arteriosclerotic group, two normals, with one death, and in the rheumatic group 25 normals, with one death.

#### SUMMARY

As a result of this study of one hundred cases of advanced cardiovascular lues, using like numbers of cases of arteriosclerotic and rheumatic heart disease for comparison, it seems quite evident that there are *no* electrocardiographic findings pathognomonic of luetic heart disease.

The electrocardiographic picture in luetic and arteriosclerotic disease shows a striking parallelism. The variations from the normal as found are due to the myocardial degeneration, and are not characteristic of the lues per se. While it is true that certain of the arrhythmias and certain abnormalities of the T-wave are of sinister prognostic import, it appears to be quite true that this is the case in the arteriosclerotic as well as in the luetic cases. There is thus no characteristic electrocardiographic picture of cardiovascular lues, and it is not justifiable to make definite forecasts of the prognosis in this disease from the electrocardiogram alone.

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## NERVOUS AND MENTAL INFLUENCES IN ANGINA PECTORIS\*†

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HEBERDEN<sup>1</sup> described angina pectoris in 1768 and referred to the nervous and mental influences preceding an attack as follows: "In some inveterate cases it has been brought on by the motion of a horse or carriage or even by swallowing, coughing, going to stool, speaking, or any disturbance of the mind." Again he says: "The angina pectoris, so far as I have been able to investigate, belongs to the class of spasmodic, not of inflammatory complaints." In a summary he notes, "the access and recess of the fit is sudden; there are long intervals of perfect health; it is increased by any disturbance of the mind; during the fit the pulse is not quickened; and lastly, its attacks are often after the first sleep, which is a circumstance common to many spasmodic disorders." He sums up and dismisses the treatment very briefly: "With respect to the treatment of this complaint, I have little or nothing to advance . . . Quiet, warmth, and spirituous liquors help to restore the patients who are nearly exhausted and to dispel the effects of a fit which does not soon go off. Opium taken at bedtime will prevent the attacks at night." He was a pioneer in the study of the complaint, wrote long before the hypodermic syringe and alkaloids came into use, and yet he made many references to the play of nervous and mental influences, the strain of effort in producing an attack, and the benefit of rest, relaxation and sedative remedies. He discovered that opium is useful in the prevention of an attack, an example of therapeutic nervous and mental relaxation.

Ottley<sup>2</sup> in his interesting life of John Hunter, who had angina for 20 years of a life noted for strain, intensity and activity, says, "The spasms about the precordia were frequently reproduced by very slight causes, as trifling bodily exertion or mental irritation. The latter cause was the most frequent, to which the uncontrolled hastiness of his temper rendered him particularly obnoxious; and so sensible was he of the risks to which it exposed him, that he was accustomed to say that 'his life was in the hands of any rascal who chose to annoy and tease him'; a painful thought, that one possessing a mind of such intellectual vigor should, from neglecting earlier to check this infirmity of temper, at length have allowed it 'so to over-master reason'

\*Read at the annual meeting of the American Heart Association, Philadelphia, June 1931.

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as to reduce him to hold his life on such a tenure." For weeks before his death, he had been in argument and open hostility with his colleagues at the Hospital and he died in a fit of temper after one of them had asked him a question. Even his face is expressive of strain and great intensity of mind. It has been the habit to interpret his angina in terms of his coronary arteries and their pathology. This coronary disease was present doubtless for years, but the frequent anger was an even greater personal pathology because it started the attack. Had he grown graciously old, and cultivated poise and courtesy instead of anger, he would doubtless have lived much longer because his angina would largely have been avoided. There is no proof that, minus high temper and angina, he would not have lived much longer, even with diseased coronaries. The angina killed him and not his cellular pathology. Many more people are afflicted with coronary sclerosis than with angina. Angina occurs without coronary sclerosis. The chest is just the bony cage that encloses the pain save that which trickles out along the nerves.

Heberden wrote very plainly about angina from his own experience and observation. He was uninfluenced by argument, instruments or the opinions of others, and the chief clinical impression made upon him by the complaint was that it belonged to "the class of spasmodic complaints," i.e., sudden, violent, convulsive, exciting, contracting, painful experiences. One may feel that he may die, and yet his pulse not be faster. With the attack he may die. On the contrary, the attack may apparently do no harm. Between attacks one may be as well as ever, only anginous. Eighty different theories exist in an attempt to explain it. "The whole history of angina from the time of the first observations down to the assemblage of volumes that have appeared in recent years is marked by the same evil—to wit, the vain pursuit of the morbid entity that lies beneath the fugitive phenomena of the syndrome." (Gallivardin.<sup>3</sup>) The trend has been to explain "the morbid entity" in terms of a cellular pathology. At one time the fad is to explain the pain in terms of too little blood to a tired muscle<sup>4</sup>; at another to say that it is due to tension and strain in an aorta damaged by a vague pathology<sup>5</sup>; and in yet another to say that too little oxygen reaches the heart muscle.<sup>6</sup> White<sup>20</sup> contrasts "coronary insufficiency" with "nervous sensitivity" as the two essential conditions.

It is well to think of the patient with angina in terms of a personal pathology. This involves a consideration of the "bad weather" and "storm" periods in the life of the patient as well as the stability or instability of his nervous life. Are the waters of his life calm and deep or wind blown and wave tossed? Nervous and mental influences hinge largely on the emotions, which in turn are related below to the instincts and above to the ways of the intellect. Emotion is hard

enough to describe. It is a fluid and fleeting thing that like the wind comes and goes, one does not know how. All the more difficult it is to describe how the mixture of instinct, emotion and mind,<sup>7</sup> fanned by strain and energy, grieved by disappointment, angered by injury or injustice, or hurried by necessity, may cause something to happen in the chest that comes convulsive and terrible like a veritable epilepsy of the circulation. Civilization as we know it in Western Europe and America, the ambition, effort and community state of mind of these areas, the increasing responsibilities that come with age, and an aging circulation, apparently are the foundations for the increasing prevalence of angina. The inner adjustment to life, the real spiritual control of life, whose outer evidence is a poise and tranquillity of mind, is not very inviting to angina and the anginous life. The strain of life and mind is probably the chief factor in producing angina and the circulatory irritability necessary to this painful complaint.

It is probably as important to realize what is not angina as it is to recognize angina. However much or little the members of the anginal family may be related to each other, each one, as in the human family, is an individual, and its diagnosis, treatment and prognosis is on an individual basis. There are many causes and varieties of thoracic pain, but only one thoracic pain which is angina. A simple grouping of thoracic pain as a working basis is valuable, and permits nervous and mental influences in angina to be more easily evaluated.

1. Angina pectoris is a paroxysmal thoracic complaint not necessarily associated with demonstrable heart or aortic disease, ranging in radiation from the epigastrium to the tips of the fingers and even more distant parts, varying in degree from a simple substernal weight or sensation, through an ache to a tearing pain or a collapsing agony, and associated in the mind with a sense of danger or dying. It occurs usually in the sensitive, nervous type, as the Jew, or in the tense, efficient American, rather than in the dull, happy negro or the calm, accepting Chinaman. There is no characteristic electrocardiogram.

2. The pain of coronary thrombosis, of a location and radiation similar to angina, but of longer duration and associated with fever, leucocytosis and often a pericardial friction rub. Much argument hinges here, but coronary thrombosis is probably a different disease from angina, and the latter is but one of the symptoms of the former. Arterial thrombosis anywhere may give pain. An infected vegetation in the pulmonary artery gives severe substernal pain.<sup>8</sup> Coronary thrombosis has a characteristic electrocardiogram.

3. The pain of acute aortitis, syphilitic or rheumatic in nature as a rule, usually substernal in location and anginal in kind. This pain is probably to be regarded as dependent on infection and a cellular pathology in the aorta, and as one of the symptoms of an acute aortitis.

4. The precordial pain of organic heart disease, valvular disease, and heart failure. It may occur in the big, brave heart of a hypertension before or after actual congestive failure. The pain may be referred rather gently to the left shoulder and arm or appear as a dull ache in the region of the left scapula. It is but a symptom of the underlying disease and failure of the heart.

5. Precordial pains usually transient, but recurring for weeks or months or even years in neurotic patients, more frequently in women. With her mind on her heart and sensitized mentally and emotionally to any thoracic sensation, she easily becomes the "false cardiopath" of the French, and is no rare patient. Some bereaved women sad of mind and weak of body, with precordial pain, the "grief ache" of the English, represent another type. Here the clinician walks cautiously in mind and manner in an effort to be sure of his conclusions, but with no physical evidence of organic disease and particularly if a tachycardia increases during the examination and a dynamic aorta pounds away in the epigastrium, with absent hyperthyroidism and tuberculosis, the whole matter is one for sympathy, psychotherapy and wholesomeness. The location of the pain is rarely substernal, more often apical or precordial.

6. There may be even more difficulty with those cases of neurocirculatory asthenia, the effort syndrome of the English, the "soldier's heart" of our Civil War. Here the evident relation to stress and fear whether in war or peace, the precordial pain, tachycardia, fatigue and even mild cyanosis, make a distinctive picture that needs time, rest and encouragement for recovery.

7. Aches and pains involving the tissues of the left chest wall. Here is a motley group geographically stimulating to a fear of heart disease. Here belong hyperesthesia of the skin, panniculitis of the adipose tissue, fibrositis of the connective tissue, myalgia of the intercostal muscles, intercostal neuralgia, and referred pain from other areas and trauma. "Would you be uneasy if the same pain were on the right side?" is a good question.

8. The pains of the grosser lesions, pericarditis, pleurisy, empyema, aneurysm, mediastinal growths, lung tumors, and referred pains from diseases of the cord and vertebra. These last are often very deliberate in intimating their location and nature.

9. Many exceedingly rare conditions occur in the chest. They surprise the clinician by their very rarity, and yet so much the more need explanation and treatment. A phlebitis of the thoraco-epigastric vein<sup>9</sup> is a case in point. Pain substernal or precordial in location is of particular importance for diagnosis.

Angina is apparently increasing in a community life of increasing strain, and it is well for the clinician to have very terse and clear

ideas about it. As he hears, as he examines, so must he think, separate, evaluate, ascribe and prescribe, and that with a very tactful and reassuring art. One of the many difficulties about angina is that it is so thoroughly subjective in its nature. One goes by what the patient says, and the patient tries to say what he feels. The patient translates his feelings into his words and objective signs of suffering; the clinician translates these words and appearances into his own interpretation. The patient must feel far more than he says to judge by his words, manner and suffering. One patient said to me, "Oh, Doctor, I wish you could see my pain, and then you could measure it and know just how great it is." One carries his emotions, feelings, prejudices, and habits about with him in a distinctively individual way. Notice how individually, proudly one describes "what I eat for breakfast every day in the year." This is probably more true of the educated and cultured than of the uneducated and natural, though to be natural may be to be very cultured. Each individual is an assortment of ways, habits and emotions, and a state of mind as well. Angina is a loose and elusive thing that comes and goes as it wills unless one gets deep into the personality and understands its very fibre and nature. The personality itself rarely understands itself, and needs rather to be understood. The structure and function of the circulation in an adult whose habits of personality are established is not to be separated from the nature of the personality, the gear of the emotional schedule, and the content of the mind. Nervous and mental influences are probably more closely connected with angina than with any other disease of the circulation save possibly the spastic condition called essential hypertension.

Angina breaks into the personality not only with pain but with the threat of danger. A friend, neighbor or relative has "had this 'breast pain' and there was something the matter with his heart, and he died with it." The fear of heart disease, the sense of dying in an attack, the danger of death are added to the cares and burdens of life. Whereas formerly he was safe, now he is unsafe; formerly well, now stricken with pain and that quickly; formerly with life ahead, now death in an attack seems very near; formerly without traffic with those distant beings called "doctors," now he sees one or more of them, needs one of them quickly in an attack, and actually has to take medicine around with him to be safe and ready to ward off the pain and the danger. I have seen a lawyer of most robust body and electric nervous system writhe in bed from attack after attack of angina until he was cowed with fear, three doctors in attendance, relatives weeping, street closed to traffic, and yet relax and soothe himself to peace with a little castor oil daily, for a foul gut, a little bromide and that in a red vehicle for sleep, and a large and gently explanatory dose of psychotherapy, all joined to wholesale faith and hope. The value of the



last two Thayer<sup>12</sup> says no one would exaggerate but a Christian Scientist. The lawyer seems to have lost his angina and is still living.

Both patient and doctor should remember that when death arrives, it has already passed. One who fears death, dies many times before he dies. Moreover, the patient realizes that he is helpless unless the doctor can help him. The doctor may tell him what the disease is, may give him medicines and accent what to do when the attack comes, but after all this is but treating the pain of the attack. It is a hypodermic for pain and nothing more. Only the anginous have angina. To have angina is to be more anginous. Merely to treat the attack is to view the patient bodily, not as a personality, and does not in the least lessen the drive of life that perhaps more than any other factor, causes the angina. It is as Houston so wisely and rebukingly says, to "practice medicine on the veterinary level." But it is another matter to treat the anginous patient for his anginous state, and to view the attack as a flash of lightning in a clouded sky. To be anginous is a state of the nervous system; to have angina is to have nerve pain in the center of the circulation. Increase the tension of the nervous system and its fatigue with a sensitive and aging vascular system in certain people, and the pain comes. We call it angina, the name of a peculiar heart pain. The doctor has much more to do when he treats an anginous patient than when he merely treats angina. He wishes to know what the anginous patient is doing to life as well as what life is doing to the anginous patient. Each person is really busy with two businesses; one the work of his life, his vocation, whereby he earns his living; the other business is just living, the business of his own life, the sum total of himself, his ambitions, endeavors, problems, and particularly their reactions. The purpose of a life is one thing and the process of a life may be quite another thing. Somewhere between the purposes and the processes of a life may be the starting point of many an angina. What the doctor does in the readjustment of the person, which includes all mental and physical processes, actions and reactions, is the real treatment of the anginous state and far more important than only drugs for angina. To treat the anginous state is the real curative and preventive treatment of the angina itself. Though the heart be the location of the attack, the nervous and mental processes may be the source of the anginous state. A case that illustrates these points may but change our clinical focus from the heart to the nervous system.

A gentleman of sixty came complaining of angina pectoris beginning with the first attack on Dec. 24, 1930, and recurring about 12 times since. The pain is substernal, though in the last four attacks it has radiated to the shoulders and down the arms to the elbows, the more painful in the left arm. There is no shortness of breath or sweating, though in the winter cold air seemed at times to bring on an at-

tack. Just stepping into a warm room would instantly stop the pain. In the last four attacks the pain came while he was walking. Recently he had been so worried, he has walked fast, intent on his business and thinking as he walked. He was of average height and build, but one was impressed with his large, fine head, his strong though anxious, worried, and tired face. His wife had telephoned ahead that he had been greatly worried for three years, and to be very gentle with him. He had noticed that an attack might be preceded or accompanied by disturbing gas in the abdomen, or the gas may come alone. The pain is worse when there is much gas.

His father died of angina at 60, though his mother lived to 88. One brother died of alcoholism and one of tuberculosis. His family has been dominant and influential for a hundred years. Many of them occupy influential positions of national importance. As a whole, it is a family of intelligence, efficiency and energy. The trick of power was in the blood and the patient confessed that he had always prided himself in taking the leading part in everything he was in. As a young man he left a small town in another state to come to Atlanta that he might have a larger opportunity to grow rich and prominent. He was a real estate broker, builder, and capitalist. He confessed that he had made and lost three fortunes. The last loss began three years ago, and for this time he has struggled to recoup and retain a little of what he had. He describes his condition quite uniquely, "For three years I have had cumulative worry. I had enough to quit and retire, and then I gritted myself into enough courage to lose. I have been gritting and losing, and now I am reacting from both. I am nervous in the sense of always being tense and straining. I have never learned to go slow and easy. When I played golf, I stepped off the tee first. When I went to church, I was chairman of the board. When I was in a conversation, I led it." There was no conceit here. It was rather the frank statement of his mental make-up. His wife was a little, thin, timid, gentle piece of steel and courage, who said, "You know, Doctor, my husband has never been able to relax and laugh. He is too serious and business-like. He is not playing when he thinks he is playing."

He was showing a lot to a customer on which he had an exclusive sale. He was suddenly told that another agent had sold the lot. He hurried to the City Hall to investigate, was angry at the injustice, and had a most severe attack. It lasted more than an hour and he was sure he was going to die. Neither warm air nor rest aided and he writhed in pain. This made him seek treatment.

Briefly, his physical condition showed one periapical granuloma, a small inactive adenoma of the thyroid, B.P. 150/100, Pulse 74, Temperature 97.5°, slight enlargement of the left ventricle, normal heart sounds, a mild arteriosclerosis, a small stone in the right kidney,

2 plus albumen in the urine, from an old prostatitis, urethritis and cystitis. All reflexes exaggerated. Hemoglobin 70. Electrocardiogram normal except for excess of somatic tremor. Gastric acidity normal. Wassermann test negative. A nervous man, and tense.

What was to be done? Was he to be viewed merely bodily? The prostatitis was very old. The dental granuloma could hardly cause this picture. Was there a common source for these three chief findings, viz., a nervous indigestion of 20 years' standing, a mild hypertension, and a more recent angina? Was the wiser judgment to regard him as a nervous American with the spasmogenic aptitude of the type, a high strung mind and nervous system, the common source for his three chief complaints; their presence the price he had paid for his efforts to lead, to dominate, and to acquire cares and riches? It seemed better to focus on his personality than on his cellular pathology. He said of himself, "My mind leaps ahead and just goes, it gets animated at the least little thing, and I catch myself halfway through an excited conversation and say, look here, this is against doctor's orders, and I must stop and get hold of my self."

It was decided to attack his personality make-up. Only the offending tooth was removed. Everything was explained to him and his wife. He was seen from April 14 to June 22, 1931, always at the office. Little emphasis was laid on the attack and much on him, his nervous system, and his high-gear living. Sodium bromide and chloral-hydrate in half gram doses were given at noon and bedtime daily. Each weekly visit was spent in psychotherapy, which is nothing more than clinical power, presence, and personality flowing through conversation, explanation, and encouragement. His wife aided greatly because the management was her own conviction approved by thirty years of married life. He became a new man in the ways of his mind, worry lessened, the attacks stopped, the blood pressure returned to normal, he slept and looked well, and only transient gas attacks reminded him of his former state. A magnesium salicylate tablet aided the nervous indigestion. The anginal attacks stopped first, then the pressure became normal, then the disturbing and prolonged gas attacks lessened. He lived by the following written directions:

1. Go slow and easy. First of all inside your mind. Second of all with your body. You have led the pack. Now fall in behind. Hurry up slower and be more backward in coming forward. He leadeth me beside very still waters. No yesterday and no tomorrow—just to live until bedtime. Few preferences and fewer prejudices.
2. Take one teaspoonful of the medicine in water at 12 noon, and bedtime, daily.

3. For the present, a warm tub bath, lying quietly in warm water for about twenty minutes, at bedtime. Temperature 90 to 94 degrees—not higher.
4. Reduce your cigarettes one a week for ten weeks beginning with ten.
5. Lie down, shoes off, coat and vest off, collar and tie off, in bed, one hour after lunch, daily.
6. Avoid, as you would a wild beast, hurry, worry, cold, cold winds, overeating, fast eating, emotion and anger. Remember Connie Mack—"Just another ball game."
7. Carry with you the little vial of nitroglycerine. Put one on your tongue and press against the roof of your mouth when the attack begins and repeat every 15 minutes until relieved. Take a tablet when it begins, and sit down. When it is over, go home and lie down.
8. Return once weekly.

This case has been to me a great clinical lesson or rather, there have been many clinical lessons in one case. From the mind and nervous system the trend to spasm apparently involved the heart in the angina, the vessels in the hypertension, and the digestive tract in the nervous indigestion. McCrae's<sup>13</sup> excellent paper, "Angina pectoris; Is it always due to coronary artery disease?" came to my mind. I could not but contrast the two cases of slowly progressive essential closure of both coronary orifices and the ability of these patients to live due to the compensatory circulation furnished by the Thesbian veins, as reported by Leary and Wearn,<sup>14</sup> with the tremendous accent the literature has laid upon the coronaries as the one cause of angina. Levy's<sup>15</sup> essay on angina as "the symptomatic manifestation of many pathological states" is a wise effort to influence the view that there may be many different causes of cardiac pain. I wondered if our nerve resections and injections, except for the relief of agonal angina after all else has been tried, is not really the wrong path for anginal therapeutics. Perhaps angina had given the clinician himself a kind of *angor animi* about the disease, and he has come to think of angina as a syndrome which has the patient instead of the patient who has angina. Conner's<sup>16</sup> recent contribution in giving graded exercises to patients with angina is a treatment of the anginal state, and an unconscious transfer of the patient's psychology from his attacks to walking, effort, and encouragement. All through McKenzie's book on Angina he touched again and again on the nervous system and the mind, but somehow he never really came near the problem, for he was too imbued with the influence of the coronaries, as Allbutt was of the aorta.

Long ago Osler<sup>17</sup> noted the rarity of angina in the run of hospital patients and in negroes. Arthur A. Stevens recently showing a case in his wards in Philadelphia, remarked, "In this and other hospitals for the indigent true angina pectoris, at least the major form of the disease, is comparatively rare. The case before us is the first I have seen in this hospital for more than a year, although in the same period there have been hundreds of patients with cardiovascular disease in its most extreme forms." Brooks<sup>18</sup> believes the condition is more frequent than in the not remote past, and that it is even increasing in the hospital class, where "it is associated with worry and great stress of life." He well says "that the obligatory demands presented to every person, physical or brain worker, is for more speed, greater production and greater stress in every relation." Morawitz<sup>19</sup> of Leipzig thinks that we should be intensely concerned with angina, for in Germany at least, one has the impression that it is daily on the increase.

Austin Flint<sup>20</sup> in a large practice in a more placid Victorian New York, claims not to have seen a case in five years. When I graduated in medicine thirty years ago, I had never seen a case, whereas now it is one of the common circulatory complaints. White<sup>20</sup> in Boston has seen as many as one hundred new cases in private patients in eight months and three new cases in a single day, which makes him "believe that the situation is appalling and demands some action on our part. Almost certainly the most effective move that we can make is to call a halt on the world's mad rush of today." Of 3,000 patients in New England seen by him, 353 or 11.8 per cent had the complaint. In estimating the value of his experience, it is only fair to say that he devotes himself to diseases of the circulation as a specialty. One wonders if this apparent increase finds its basis merely in a pathology of the coronary arteries. One of my colleagues, L. M. Gaines,<sup>21</sup> has had here in Atlanta, four women, all under concurrent treatment. I knew one of them for many years, and her nervous make-up was identical with the case above described. Such nervous systems could well be described as electric, extravagant, or by the colloquial word, "spark-ing." They are up and at life by day and night on every occasion and incident.

As hypertension has apparently increased, so has angina. In 1931 in Atlanta, among the better class of whites, particularly over fifty, it is common. Among the negroes subject to every form of cardiac and coronary disease except the influence of nervous and mental strain, it is practically unknown. The negro has far more circulatory disease than the white, added to exposure and the carelessness of a careless race, and no angina. I worked twenty years among sick negroes in both in- and out-patient sections, and never saw a case in a negro. Among approximately 20,000 in-patient negroes in Atlanta, a diagnosis of angina had been made, even by the interns, only five times

in nine years. The staff had never made the diagnosis in a negro. In a study of these five charts bearing the diagnosis, no one is characteristic of the syndrome but rather of coronary thrombosis, acute fibrinous pleurisy, precordial distress from congestive failure and apical distress from religious and musical fervor. Lyons<sup>21</sup> in New Orleans, thinks it may occur occasionally. Musser,<sup>21</sup> in the same city, has never "observed a full fledged, typical attack of angina pectoris in a negro. On the other hand, we frequently see negroes who suffer with cardiac pain but not the definite anginal syndrome." Lemann,<sup>21</sup> in the same city, with an enormous experience and interest in this question, has never seen true angina in a negro, and makes these interesting comments, "I have no explanation for this very striking discrepancy which has engaged our interest and attention for many years. The only probable explanation that comes at once to my mind is the fact that negroes seem to be less highly organized nervously. They seem to bear pain better than do the whites. Has it not also occurred to you that suicide is exceedingly rare, almost unheard of, among negroes? In other words, I am suggesting that while the physical basis for angina and coronary disease is certainly present in negroes, the symptom complex is not present because of the less acute perceptions of pain. I acknowledge that this is not a complete and adequate explanation."

I questioned a very sensible negro about suicide in his race. He said it was not true that the negro did not worry very much. At times there was great worry, but he never worried very long about any one thing at any one time. It was difficult for the negro to worry standing up, and when he sat down he went to sleep so easily that the worry passed away. This discussion concerns only the full blooded negro. Another negro stated that the chief difference between the white man and the negro was that the white man knew how to work but that he did not know how to play. All of this means that the average negro never takes anything very seriously for very long.

W. R. Houston,<sup>21</sup> in Augusta, has never seen angina in a negro apart from the substernal pain in a luetic aortitis, which removes it from our consideration. Stone,<sup>21, 24</sup> of Galveston, writes, "I still have to say that I have yet to see a typical case of angina in a negro." Comparing his cases with those of Wood, Jones and Kimbrough<sup>22</sup> from Virginia and Massachusetts, "It is noted that there are only about one fourth as many cases of angina pectoris among the Texas group as were reported from the two more northerly situated states." George Herrmann,<sup>21</sup> from a large experience, has never seen a case in a negro. J. D. Odum<sup>21</sup> studied the question for me in the Canal Zone and Panama, and found from the records of the Gorgas Hospital, angina listed as a principal disease with five cases among the whites, and two deaths; West Indian negroes, three cases and two

deaths; and not a single case in a negro in the hospital for this year up to May 13, 1931. Whether these cases were essential angina pectoris or dependent upon aortitis or coronary thrombosis was not stated. Among the Indian tribes in Panama, there is no record of a single case. Deaths from angina apparently are nearly twice as frequent in the northern and eastern states as in the southern and mid-western states, and the rarity of angina in the slow-going tropics is well known. The relative rarity in women is notable and suggestive.

The white man, particularly those living lives of stress in urban conditions of competition, work and strain, makes his little plans and lays up cares and riches and takes much thought of the morrow; the negro knows his weekly wage is his fortune, takes each day as it is, takes little or no thought for the morrow, plays, and lives in a state of play, hurries none and worries little. What must it be to live unhurried, unworried, superstitious but not ambitious, full of a child-like faith, satisfied, helpless, plodding, plain, patient, yet living a life of joy and interest? Even the negro child laughs easily, dances, sings, plays, and that usually in rags and wretchedness. Neither does the Chinaman have angina. He has the placid inner life of the Oriental, reinforced by thousands of years of custom and inner peace, and accented by his nature, "this tranquil quietist." Contrast these two sentences from Houston,<sup>10</sup> "Ah yes, the Chinese lack the spasmogenic aptitude—placid, gentle, peaceloving, Buddhist—their ideal, the serene calm of Amida Buddha, with closed lids and folded hands—symbol, the lotus flower scarcely swaying over the still pool." Such is the Chinaman; now for the American. "It is easy to see why the red, hairy, wassail-quaffing, fighting barbarian from the west has the spasmogenic aptitude ready set upon minimal provocation to tighten its coils on him."

In the midst of writing the above in my pleasant, airy room, the phone rang. It rang again, and then again. The Ethiopian maid downstairs very near it, apparently did not hear it, moved not, nor paid it any mind. And why should she hear it? She was in a music land, crooning and singing over her work. Upstairs I was interrupted. Here was a paper, I must finish it, office hours at one—why doesn't she answer it? I tighten with the spasmogenic aptitude, and answer it resentfully. A call from another maid in another home. I tighten another resentful notch, call the maid, upbraid her for her indifference to a sound which by habit, courtesy and necessity I cannot be indifferent to, return to the typewriter, react and smile and try to relax, while the maid went on with her childish talk in ignorant tidbits, utterly oblivious to time, duty and scolding. I try to correct, she accepts. She accepts so habitually that she neither replied to my scolding nor cared to explain. I strain, she lives with the day. She illustrates the advantages of being uneducated, untutored, unambi-

tious, just one who has by nature been born with "an internal adjustment—to change her soul into an attitude of acceptance." But I meet difficulties every day, and many times a day, and try much or little to change and correct the difficulty externally rather than to adjust myself to it internally. The executive said daily to his secretary when he sat down to answer the morning mail, "Bring on the daily grief and let's do the best we can to settle it." It is a habit of life, and finally the nervous system and the circulation can no longer *together* meet the strain, and the patient has angina.

We call a syndrome essential angina pectoris, or essential hypertension, or nervous indigestion, but in reality it can be explained on the basis of the spasm of muscle in different systems dependent not primarily upon an organic or cellular pathology of that system, but rather upon the spasmodic aptitude and constitution of the individual. As is the gear of the nervous system, so is the presence or absence of spasm. "When I look back over the patients I have seen suffering with the benign anginas, it has generally been true that they have had other spasms." (Houston.) A useful illustration that affords rich analogies is congenital pyloric spasm and stenosis in infants, and particularly in the latter. It has as pure a functional pathogenesis as we know, and occurs before individual habits and mental processes can have little, if any, influence. On the other hand, its presence or absence should be indicative of the spasmogenic aptitude characteristic of the race or tribe to which the newborn belongs. Its occurrence may be a measure of the racial gear, and points towards the spasmogenic trend. Among 24,000 Chinese patients analyzed for Houston in The Peking Union Medical College, only one per thousand suffered from evidence of spasm of unstriped muscle. There was only one case of pylorospasm in a premature infant, not one of stenosis, and only eight in adults, that could be called functional. It is to be remembered that the Chinese in their own country do not have either essential angina or essential hypertension. Pyloric stenosis involves smooth muscle, and partakes of the nature of the "spasmodics" as Heberden said of angina. Jacobson's<sup>23</sup> studies afford evidence that "muscular activities are an index of the activities of the nervous system," and this applies to smooth as well as to striped muscle. Further, the tonus of smooth muscle seems to influence striped muscle and vice versa. The tonus of skeletal muscles is increased with the gastric hunger contractions of smooth muscle. Racial susceptibility to the spasmogenic aptitude throws a new light not only on pyloric stenosis, but upon angina, hypertension, nervous indigestion, and other spasms.

The infrequency of pyloric stenosis in the negro as compared with the white child has often been mentioned in pediatric literature. Dr. M. Hines Roberts<sup>21</sup> furnished me with the statistics from three pedi-



atric services in Atlanta. The Grady Hospital receives only white children; the Emory Grady only negro children; and the Eggleston Memorial receives only white children.

Grady Hospital, In-Patient.—5400 white children in 7 years. Pyloric stenosis, 6 cases.

Emory Grady Hospital, Out-Patient.—13,248 negro children in 10 years. Pyloric stenosis, no case. Pyloric spasm, 5 cases, two in infants almost white in color; of the other three only one vomited enough to be classed as a true pylorospasm. Complexion unknown.

In-Patient.—3,439 negro children in 10 years. Pyloric stenosis, no case. Pyloric spasm, no case.

Eggleston Memorial, 2228 white children in 3 years. Pyloric stenosis, 8 cases. Pyloric spasm, 8 cases.

The pediatrician classifies pyloric stenosis as a disease of modern times with a notable increase in the number of cases in the last thirty years. The internist can bear witness to the increase in the number of cases of angina, hypertension, and nervous indigestion among the white races of Western Europe and North America. These two witnesses bear witness to the strange rarity of these three conditions in the negro and the Chinese. The psychology of stress, strain and struggle in the white races is in sharp contrast to the humorous carelessness of the musical negro or the placid acceptance of the gentle Chinaman. The white race talks of speed and records, domination and colonization, drives, rallies, sales and sales-resistance, estates, trusts and results, it increases its effort and income to gratify its desires, and then multiplies its desires. We call it progress and western civilization. The Chinese and the negro accept and, perhaps far more than the white man, conquer both their spirits and their nervous systems. In this sense the white man's burden is his nervous system. We have so far done very little either for angina or hypertension. We have been very gullible about angina. We have viewed it with the credulity of tradition and treated it with the fatuity of empiricism. There is an empiricism in etiology as well as in therapeutics. The conception of the problem as one of racial susceptibility intimates how limited our studies have been. Perhaps when we realize the tremendous power of nervous and mental influences to produce the anginal state as well as the anginal attack, we shall be stimulated to accent the former rather than the latter, and at first at least look for the cause of both in a personality pathology. Then we may accomplish more for the patient. Spasm is a very old-fashioned word. Personality pathology

may take much deep and tactful wading. The patient is far more than a mere body of tissues and organs. The nervous system and the mind, with their trains of emotions and instincts, may give a very real etiology.

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## CONTRIBUTORY FACTORS IN CORONARY OCCLUSION\*

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IN ALMOST every instance the ultimate cause of occlusion of a coronary artery is sclerosis of the vessel wall;<sup>1, 2, 3, 4</sup> endarteritis obliterans and embolism constituting but rare exceptions to this general rule. Whitten<sup>5</sup> finds that the arterial branches supplying the left ventricle leave the main stem at right angles and pass directly through the musculature, while those to the right ventricle enter the muscle more obliquely. He believes that this different relationship explains the more frequent occurrence of thrombosis in the left ventricle, kinking and consequent vessel wall changes in the main stem being promoted there by the anchoring effect of the branches. This, however, does not explain the presence of sclerosis in the arteries supplying the left ventricle of one patient and its absence in those of another. When the causes of arteriosclerosis in general and of coronary sclerosis in particular have been discovered, obviously those factors which contribute to sclerosis will be recognized as important contributory factors in coronary occlusion, but at present they cannot be evaluated. Whatever its ultimate cause, it is clear that once coronary sclerosis has been established secondary factors frequently contribute to produce thrombosis. The incidence of occlusion does not parallel the extent of coronary sclerosis. Many patients with extensive vessel change never experience clinical occlusion. Occlusion occurs, on the other hand, in individuals showing little evidence of coronary disease.

Careful study of case reports offers, perhaps, the best means of determining precipitating causes and of evaluating their relative importance. Published reports, however, having been concerned particularly with the clinical manifestations and the course of occlusion, too often unfortunately, furnish an incomplete history of the patient and omit details attending the onset of thrombosis. This defect applies also to my own records, so that in reviewing them together with published cases it has been impossible to tabulate completely all data that might bear on the problem. Certain findings, however, appear to be significant.

*Relationship to Infection.*—The notion has long been widespread that infection in some way predisposes to occlusion. Opinion at

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\*Read before the American Heart Association at Philadelphia, Pa., June 4, 1931.  
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present is not altogether in agreement upon the matter, but those who report large series of cases find little evidence that infection, either acute or chronic, contributes toward precipitating thrombosis, except in rare instances.<sup>1, 2</sup>

*Relationship to Angina Pectoris.*—One relationship is at once apparent. Most patients with coronary thrombosis have had attacks of pain conforming more or less typically to angina pectoris. Of Parkinson and Bedford's<sup>1</sup> patients only 38 per cent had had "no previous angina." Levine<sup>2</sup> states that the "great majority of patients had definite angina pectoris antedating the attack." The close etiological relationship between coronary occlusion and angina is further evidenced by the high incidence of occlusion in patients with angina. This is given by White<sup>4</sup> as more than 26 per cent. Even though it may appear that attacks of angina upon occasion may be produced by causes other than arterial,<sup>6</sup> the evidence accumulates that anoxemia of heart muscle resulting from deficient circulation is the basic factor in the vast majority of cases. Evidence becomes increasingly impressive also, that in most instances this deficiency of the circulation results from coronary sclerosis.

So far the relationship between occlusion and angina pectoris is referred to the ultimate cause of the two phenomena rather than to the precipitating causes of occlusion. It is well known that the precipitating causes differ. But this very difference between the factors which precipitate thrombosis in a sclerosed coronary artery and factors which produce a temporary insufficiency of the circulation in such arteries, throws much light upon the mechanism of thrombosis and indicates certain contributory factors in its occurrence.

*Factors in the Production of Pain in Angina.*—The mechanism by which pain results from inadequacy of coronary flow is not a proper concern of this paper. It must be kept in mind, however, that circulatory insufficiency may be absolute or relative, its duration variable. So far as anoxemia is concerned, transient diminution of blood supply would produce the same result as temporary increase in demand for oxygen. The same result, indeed, would be produced by increase both in demand and in coronary flow provided the increase in blood flow did not keep pace with the demand. Any factor, therefore, which either increases the need of heart muscle for blood or diminishes the coronary flow might produce pain. Anything which increases coronary flow but which at the same time increases more the demand for oxygen might also produce pain.

*Factors in the Production of Thrombosis.*—Except in cases of embolism, thrombosis ultimately depends upon a lesion in the vessel wall. Possible contributory factors are: (a) a slowing of the circulation and (b) change in the character of the blood. In sclerosed coronary arteries, therefore, any influence which might lessen coronary flow or

anything which might change the blood itself so as to make it more easily coagulable might conceivably precipitate occlusion. Mere increase in need for oxygen unaccompanied by diminution of coronary flow, however, does not favor occlusion, nor does increased oxygen want when accompanied by increased coronary flow; both of which effects may produce angina. Since embolism is a rare cause of coronary occlusion and since lesions of the intima are almost invariably present in patients who experience this accident, study of contributory factors in coronary thrombosis becomes essentially a study of those factors which diminish coronary circulation and of factors which might make the blood more readily coagulable. Review of case reports reveals little evidence suggesting such blood changes. But it does reveal evidence of factors which lessen coronary flow.

*Control of the Coronary Circulation.*—Anrep and Segall<sup>7</sup> find that in the denervated heart coronary blood flow is regulated entirely by the mean level of arterial pressure, principally by the diastolic level. As diastolic pressure rises coronary flow increases, and vice versa. In the enervated heart, however, change in diastolic pressure, while important, is not the only factor regulating coronary flow. In the heart-lung-brain preparation the flow varies also with variation in cardiac output. It is independent of strength of contraction. This variation in coronary flow with systolic discharge Anrep and Segall attribute to a reflex mechanism through the vagus. When the vagi are cut, volume flow no longer varies with change in output. Stimulation of the peripheral end of either vagus then diminishes coronary flow. These authors reach the conclusion that constrictor fibres are carried by the vagus, dilators by the sympathetics. The rich vagus and sympathetic nerve supply to the coronaries has been beautifully demonstrated by Woolard.<sup>8</sup> Segall<sup>9</sup> and Cruickshank<sup>10</sup> both state that this reflex dilatation of the coronaries with increase in systolic output plays an important part in adapting the heart to the necessity of increased work.

Possible factors in the diminution of coronary flow, then, are the following: (a) lowering of diastolic pressure, (b) lessening of cardiac output, and (c) coronary constriction by vagus stimulation. Any circumstance which might be suspected of contributing toward coronary thrombosis, must be examined particularly with reference to the probability of its producing any of these effects.

*Circumstances Attending the Onset of Thrombosis.*—The initial evidences of coronary thrombosis rarely appear during unusual effort or excitement, circumstances which characteristically produce angina. Details of onset are given in only 81 cases of Parkinson and Bedford's series. In none was unusual exertion recorded. In a little more than 40 per cent the pain began while the patient was asleep or in bed, "often in the early hours of the morning," and in 32 per cent more

there was no relationship to exertion. In the remaining 27 per cent it began during exertion, but in no instance was the exertion of unusual form.

This almost invariable absence of effort in the onset of thrombosis and its conspicuous association with rest cannot fail to be significant. By far the most common circumstance of onset is during sleep, particularly in the early morning. This is precisely when diastolic pressure is lowest and systolic output smallest. Grollman<sup>11</sup> finds that the blood pressure (both systolic and diastolic) and the cardiac output in sleeping subjects fall progressively until about 4 A. M. Whether this is due to the prolonged rest or to the low phase of a diurnal rhythm, he does not attempt to say.

Lowering of the diastolic pressure as the precipitating cause of occlusion is strongly suggested in the following case:

A woman 45 years of age was examined before operation, not because of any suspicion of abnormality of the circulatory system, but as a routine preliminary. Aside from a blood pressure of 160 mm. systolic and 90 mm. diastolic nothing to attract attention was observed. Just before operation morphine, gr.  $\frac{1}{4}$ , was administered, and a few hours later this was repeated. A widespread urticaria rapidly appeared, a result which, it subsequently developed, had previously followed morphine administration. Her blood pressure had fallen conspicuously before the second dose and after that there was a further decline. For seventeen hours frequent readings showed a variation of the diastolic pressure between 30 and 50 mm. A few days later she began to complain of substernal pain. There was a rise of fever, a moderate leucocytosis and a secondary drop in blood pressure. The electrocardiogram showed a deep Q-wave in Lead III with a plateau type of T-wave, features which changed in subsequent records. The interpretation was as follows: Thrombosis of a small coronary artery induced by slow coronary blood flow incident to the prolonged low level of diastolic pressure.

*Opposing Factors in Thrombosis and Angina.*—Just as lowering the level of diastolic pressure and lessening cardiac output, by diminishing coronary flow, must be regarded as important factors in precipitating thrombosis in the case of an individual with sclerosed coronaries, so in the same individual those influences which raise diastolic pressure and increase systolic output, thus increasing coronary flow, must be considered as lessening the probability of thrombosis. Exertion and excitement are such factors. But while increasing coronary circulation they also increase the need for it, and in individuals with coronary sclerosis the heart muscle may still be inadequately supplied with blood. A patient with coronary disease, therefore, gets angina with exertion, thrombosis while at rest.

It has been noted by many observers that coronary occlusion and thrombosis in other arteries as well, is relatively frequent in patients in the later stages of heart failure. Most authorities believe that systolic output is diminished in this condition. The enforced rest contributes toward the same result. Although it is possible that other fac-

tors promote thrombosis in heart failure, it appears that diminution in coronary flow is a contributory influence.

*Vasoconstriction.*—The remaining factor which has been shown experimentally to impede coronary circulation is vasoconstriction. Whether or not it is a clinical factor must at present constitute a theoretical problem. If reflex coronary constriction occurs clinically, in cases with impaired coronary circulation the constriction might cause angina, or the coronary lesion might be so extensive that the added factor of constriction somewhere in the arterial tree might be sufficient to precipitate thrombosis. There is much suggestive evidence that it produces these effects. Segall<sup>9</sup> believes that "coronary artery spasm due to central or reflex stimulation of the vasoconstrictor mechanism must be seriously considered and studied as a possible cause of certain types of angina pectoris." This is no new conception. Mackenzie<sup>12</sup> says: "That angina pectoris is the outcome of a stimulation of the central nervous system is so manifest that it needs no comment."

The evidence that the precipitating cause both of angina and of thrombosis frequently is referable to the *gastrointestinal tract* is impressive. In case reports of both, references to indigestion and to the relationship of onset to the preceding meal are conspicuous. Walking, particularly "after a meal," receives special mention by Mackenzie and by McCrea,<sup>6</sup> and by many others as a common cause of angina. Hamman<sup>13</sup> says: "Patients with angina pectoris mostly ascribe their symptoms to indigestion and tell in detail how abdominal distention precipitates the pain, which quickly disappears as gas is eructated." It can hardly be fortuitous that similar references appear in comments upon thrombosis. Levine<sup>2</sup> says that "it frequently occurs during rest, while sitting quietly in a chair *at a dinner table,\** or during sleep." Parkinson and Bedford<sup>1</sup> state that "many patients are aroused from sleep by pain, or are seized with it while sitting quietly at rest, *after a meal\* . . .*" Of the eight cases reported by Werley<sup>14</sup> such references occur in six. In two cases the patient "ate heavily" during the meal before the attack. In another, the attack occurred "just after lunch." Another patient died suddenly "after supper."

None of these authors specifically refers the onset of occlusion in any case to the gastrointestinal tract; yet each mentions digestion or digestive disturbance, and by inference each has been impressed by possible relationship between gastrointestinal influences and the development of thrombosis. This suggestion has arisen time and again in my own cases. In many instances the patient has attributed his attack to a particular article of food, to a midnight supper or to long standing indigestion. The matter can hardly be dismissed with the observation that the subjective sensations in occlusion are similar to those produced

\*Italics—mine.

by indigestion and that the patient confuses cause and effect. Upon occasion it may be that it is not in the mind of the patient that confusion exists.

If gastrointestinal reflexes upon occasion do lessen coronary flow enough to cause angina or to precipitate occlusion, vasoconstriction must be regarded as the responsible mechanism. Although reflex coronary constriction has been demonstrated, and by the authors quoted above is thought to induce angina; and although evidence is presented in case reports that gastrointestinal reflexes may precipitate both angina and thrombosis in this way, direct proof that coronary constriction may actually result from visceral stimuli appears to be lacking. Other cardiac effects, however, are known to be so produced. That irregularities so arise has long been the conclusion of clinical experience. Pearey and Howard<sup>15</sup> produced extrasystoles and changes in the ventricular complex by visceral stimulation in dogs, the apparent pathway being via the sympathetics. Hewlett<sup>16</sup> attributes "vagus slowing of the heart

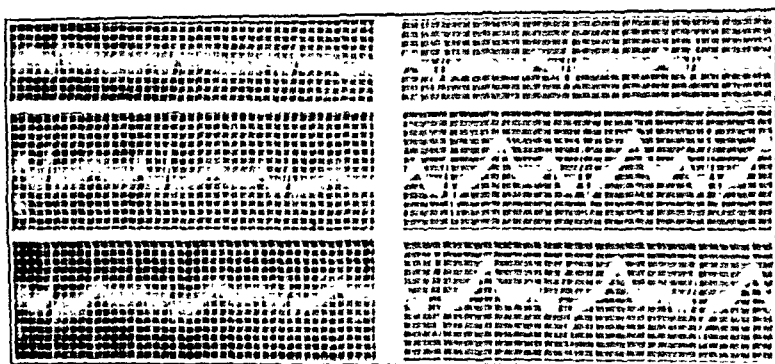


Fig. 1.—Electrocardiograms of the patient in Case 1. At the left is the record made by Dr. Fuller in August, 1929, following the attack. At the right is the record made in November, 1929.

to reflexes that arise from the abdominal viscera." Whatever the reflex path, it would appear that gastrointestinal stimuli as the precipitating cause of coronary occlusion must be carefully considered.

*Cold.*—Pressure upon the heart through the diaphragm by a distended viscus has long been suspected of producing certain cardiac effects. Pearey and Howard<sup>15</sup> present evidence that these effects result from reflex stimuli rather than from displacement. Another direct factor, however, must be considered, i.e., *cold*. In two of our cases the evidences of occlusion immediately followed the drinking of cold fluid.

CASE 1. A man 45 years of age, in good health, in August, 1929, was about to start on an automobile trip. He drank several glasses of ice water and began to belch, to "get his breath hard," and to experience a sensation in the chest which he found it hard to describe. Dr. James T. Fuller, who was called, made a diagnosis of coronary occlusion, and treated him on that basis. A part of the electrocardiogram made by Dr. Fuller at the time is shown at the left of Fig. 1. The R-T configuration in Leads I and III is that which characteristically is shown in oc-



clusion involving the apex or anterior part of the left ventricle. In our record of November 29, 1929, shown at the right of Fig. 1, changes have occurred. The patient at the time of the second record was quite well. He had had occasional sensations in the left chest and had noted a few extrasystoles, but has since been in good health.

CASE II. A man of 55 years had always been in good health. Frequent examinations for insurance had disclosed nothing of importance. In July, 1930, while driving in an automobile early one evening he drank a cold beverage and began to experience "heart burn." After about twenty minutes there was severe pain in the upper mid portion of his chest, down both arms and into the neck and right shoulder. There was profuse sweating, dyspnea and slight nausea. When examined a few hours later, he was pale and was still in severe pain. The heart action was rather slow and there was an irregularity which appeared to be of sinus origin. There was no fever. The blood pressure was 140/85 mm. There were no abnormal signs on examination of the lungs and abdomen. Morphine sulphate, gr.  $\frac{3}{8}$ , gave considerable but not quite complete relief, and next morning he still had some pain. The blood pressure then was 110/70 mm. and the mouth temperature was 99.1°. A

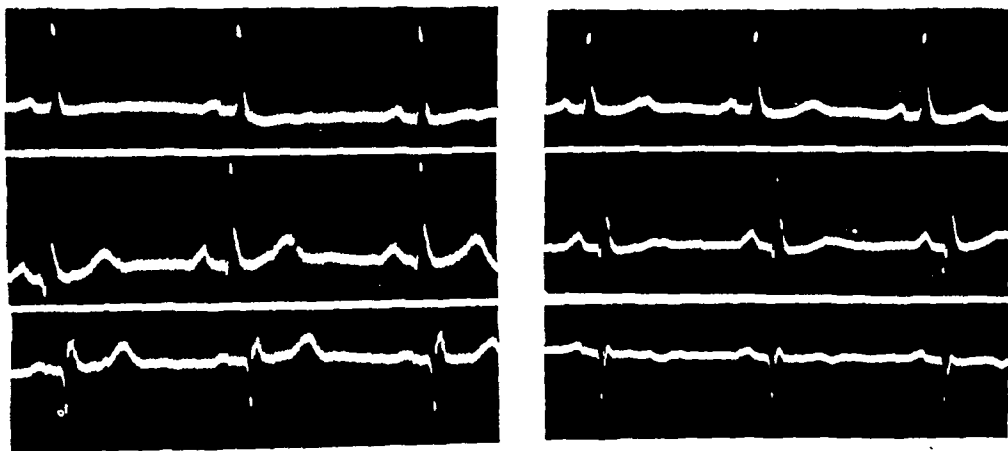


Fig. 2.—Electrocardiograms of the patient in Case 2. The record made one day after the attack is shown at the left. That at the right was made seven days after the attack.

few days later he again experienced some pain for a short time. After that recovery was uninterrupted and except for a feeling of weakness there were no symptoms. Fig. 2 shows the differences in electrocardiograms made one and seven days after the attack respectively. The change in the T-waves of the first and third leads was further accentuated in a later record. The patient has since remained quite well.

It cannot be proved that the occurrence of coronary occlusion with the ingestion of cold fluid in these two cases was other than a coincidence, but in both cases the suspicion of cause and effect must be great. If cold in the stomach precipitated the occlusion, two possibilities must be considered, (a) reflex coronary constriction and (b) the direct effect of cold upon the heart.

*The Direct Effect of Cold.*—Wilson and Finch<sup>17</sup> observed inversion of the T-waves in Lead III of the electrocardiogram in men after drinking three glasses of iced water. X-ray pictures showed that the in-

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Wearn's belief that those agencies which lead to arteriosclerosis presumably play a more or less indirect rôle in causing cardiac infarction. Thayer<sup>7</sup> pauses in his busy life to reflect on angina pectoris, but does not do more than stress the prognosis and treatment of this particular condition, without mentioning coronary occlusion. Riesman,<sup>8</sup> writing in the same year in the *Medical Clinics of North America*, reports upon the first cases we can find in which there was some attention paid to the familial incidence of the disease. He states, however, "As for the etiology of coronary thrombosis, it coincides with that of coronary sclerosis, and about that we know all too little. Syphilis is not a factor of importance, but tobacco is . . . ."

Gordinier,<sup>9</sup> in a report of thirteen cases, mentions only one case, Case 3, in which there was any family history of importance. In this particular instance he states that four brothers died of angina pectoris, all of whom apparently died as a result of occlusion of the coronary artery. Christian's article one year later (1925)<sup>10</sup> does not mention the etiology and does not detail case histories in the 70 cases that he reviewed. One feature is of interest in this paper, however, in conjunction with our later discussion of the etiology of the condition, namely that there were 32 patients that were under 60 years of age who died a coronary death. In 1926 Hamman<sup>11</sup> discusses the antecedents of patients who have coronary occlusion. He states that occupation, habits, station in life have no direct bearing upon the condition, but that coronary disease is particularly common to men of intellectual habits and to men who have held positions of responsibility and importance. He rather accentuates the concept that those who are intellectually alert are more keenly sensitive to pain than the so-called lower classes, although the dramatic manifestations of coronary occlusion occur equally often in all.

In 1927 Frothingham<sup>12</sup> gives the details of a case of coronary thrombosis which was of interest because it occurred in a relatively young man who had no previous indications that he was a sufferer from vascular disease. Here we have direct evidence of familial tendency of the disease because in this patient the story goes that his father died at the age of 64 of what was undoubtedly coronary thrombosis, although at the time it was called acute indigestion. Greenberg<sup>13</sup> writes entertainingly of the causation of coronary disease. "Fascinating as it is, to speculate about the cause for things in general, the cause of this disease is no better known than the cause for arteriosclerosis elsewhere in the body. Of the usually mentioned causes, faulty diet, focal infection, alimentary toxic products, metabolic waste products may be dismissed as platitudes. It is possible that hereditary influences play a not unimportant rôle especially under the strain and stress of modern life. Syphilis, diabetes, among the chronic diseases cannot be entirely dismissed as contributing factors. Experiments

with bacterial toxins have yielded no positive results. One must maintain an open mind as to the cause of this disease until better proof is adduced."

It will be observed that the factor of heredity is beginning to be recognized by authors who are reporting upon coronary occlusion. Barker,<sup>14</sup> writing the latter part of this same year, says that undoubtedly there are certain families of certain races who are more subject to coronary thrombosis than others. He calls attention to the fact that the Irish people are relatively free from angina pectoris and coronary occlusion as contrasted with the English, stating that possibly diet, which has been held accountable in the past for this racial difference, may not play as important a rôle as inherited racial predisposition. Although articles appearing in periodicals had begun to stress this factor of familial incidence of the disease, two books on diseases of the heart which came out in 1925 and 1926, respectively, one by Cabot, the other by Vaquez, make no mention of familial incidence of coronary obstruction. Christian<sup>15</sup> in the following year, in discussing the etiology of coronary infarction, mentions that there is often an arteritis of inflammatory nature, sometimes caused by syphilis and at other times by bacterial infection, stating that he believes that arteritis of infectious diseases may play an important causal rôle in cases of infarction as expressed in younger individuals.

The growing appreciation of the important factor of heredity in the production of coronary occlusion is exemplified by conclusion 5 of the summary from Levine and Brown's<sup>16</sup> splendid monograph on coronary thrombosis. They state that hereditary factors, although extremely difficult to analyze, were found to be most important, especially in those patients who have coronary thrombosis at a comparatively young age. Possibly as a part of the hereditary factor there seems to be a certain type of individual who is more apt to develop the disease. They state, furthermore, that "arteriosclerosis is a very rare finding and in some it was limited to the coronary arteries." Also they comment upon the rarity with which syphilis may appear in relationship to the condition and likewise the etiologic insignificance of other infectious diseases.

Wilson<sup>17</sup> wrote last year on angina pectoris and coronary thrombosis as observed in 93 patients. As he expresses the difference between the two conditions, coronary thrombosis may be the most severe expression of angina pectoris. In the etiology, infection seems to play an important part, syphilis not so important, while "a familial tendency may also be in evidence."

Two recent articles in English literature are of exceedingly pertinent interest in relationship to our present theme—that coronary arterial disease exhibits a remarkable familial tendency. Herepath and Perry<sup>18</sup> write that their subsequent report is presented largely with

the hope of eliciting from family practitioners notes of similar cases. In the present instance they report the death of a father at the age of 42, who died suddenly and whose two brothers likewise died sudden deaths—one at the age of 30 and the other at the age of 31, one of whom came to autopsy and was found to have atheroma of the coronary arteries. The third brother died suddenly a month after physical examination. In this case there was the story of anginal pains, although the physical examination, including x-ray of the heart, was normal. Peripheral arteries were not thickened and the blood pressure was 120/70 mm. The electrocardiogram, however, showed the changes of coronary arterial disease. The authors state that the pathological process explaining the death of the patient was a premature senility of the arterial tree, in this particular instance in the coronary arteries, without any evidence of an infective factor. The second paper, by Coombs,<sup>19</sup> has some statements with which we are thoroughly in agreement. "The familial incidence of angina pectoris is well known." He mentions a family of father and four children, all of whom died of coronary disease. In his present series of cases he mentions instances of cardiac infarction in which "there were two pairs of near relatives. One of these pairs consisted of father and son." Particularly striking to us are these statements: "There are two possible interpretations of this familial incidence. One is that it is nothing more than an example of the well-known liability of certain families to arterial degeneration, a liability which is apt to be particular as well as general since it includes a predilection for certain vessels. For example, there are families whose members all die of cerebral hemorrhage. Another suggestion is that aberrations of the coronary arteries which, as Hadfield has pointed out, may throw an undue measure of responsibility on the one trunk, may run in families." Coombs concludes, furthermore, that of the three great infective diseases of the heart, none of them excites the coronary syndrome except extremely rarely. Cardiac infarction, for example, in cardiac syphilis, was observed only once in 88 cases.

The latest book on heart disease, that of Paul D. White,<sup>20</sup> in discussing the etiology of coronary disease and coronary thrombosis, states that faulty metabolism, overwork, high protein diet, infection and heredity are among the many factors suggested, but none has been proved or even consistently found. Farther down in the same paragraph he states that the influence of heredity is supported by the frequent finding of several members of a family with coronary sclerosis.

From the review of articles which have mention in them of the etiology of coronary disease and from the review of other articles which are by men of reputation and authority, it is evident that heredity is coming to be looked upon as a rather important factor in the etiology

of coronary disease. We have called attention to the observation of Coombs, and we are heartily in accord with his conception, that aberrations of the coronary arteries may throw an undue measure of responsibility on the one trunk and that these abnormalities may run in families. We believe that there exist two distinct clinical divisions of coronary occlusion: the one, the occlusion that occurs in old individuals, which is merely part and parcel of the general syndrome of arteriosclerosis and in which those various indefinite, vague and irregular pathogenetic factors operate which are presumably responsible for the arteriosclerosis which exhibits a general sclerosis of all the vessels of the body. On the other hand, there exists a certain group of individuals who die at a relatively early age of coronary occlusion. These individuals do not have hypertensive heart disease or at most have a relatively slight rise in systolic and diastolic blood pressure. They have not had arteriosclerotic heart disease as ordinarily conceived, nor peripheral arteriosclerosis, but they do possess a peculiar liability for degenerative changes in the coronary vessels and they show a peculiar and marked familial tendency to sudden death, which death, of course, occurs presumably as a result of the cardiovascular accident of coronary occlusion. It is in this type of individual, as we have indicated several times in our review of the literature, that this catastrophe occurs when they are under 60 years of age; usually they are people who have always had excellent health, who have never had syphilis or rheumatic fever or other severe infection and who have led active, busy lives.

In substantiation of our conception of this rather sharply defined division of types of arterial occlusion, we would submit a brief account of the family history of Mr. W.:

This patient died in the fifth decade of life. He had always been an active, hard-working, professional man, free from illness, with a blood pressure that averaged 130 to 140 mm. systolic, and who had no evidence whatsoever of peripheral arteriosclerosis. Abrupt death was preceded by about six months of angina-like attacks. Death was relatively sudden and at autopsy the explanation was as obvious as the clinical syndrome; there was a large area of recent infarction in the cardiac musculature. The father of this man died as a result of sudden heart failure. He likewise had been an active, mental and physical worker. He died at the age of 55 years, following a sudden heart attack. His first cousin once removed, who also was a professional man, died when he was slightly past 50 years of age, likewise of what was called then angina pectoris. Death was sudden. Three cousins of the first patient also died in exactly the same way—a sudden death, as far as we can find out in the several instances, with previous anginal attacks which were followed by sudden death. All of these individuals, according to the accounts we can get from present members

of the family, were strong, healthy, active individuals who had very much the same general habitus, slightly overweight, well set up, of short stature, and capable of prolonged and continuous mental and physical effort. These are the definite instances of sudden death that we have been able to obtain in this family history of Mr. W. There is no question as to these facts; but we can add, moreover, that from information from the relatives it is possible that other members of the family may have had a coronary occlusion to cause their death, because two of the immediate forefathers of Mr. W., a grandfather and a granduncle, are said to have died suddenly, but we could find no one who could definitely establish this fact other than through hearsay.

*Conclusions.*—The thesis has been advanced that there are two quite distinct expressions of coronary occlusion. The one is observed in elderly individuals, possessors of a well marked sclerosis of the arterial tree as a whole and in whom the etiological factors are those of arteriosclerosis in general and represent largely the effects of senescence. The other occurs in men, as a rule, not past the sixth decade of life who do not have generalized arteriosclerosis, who may have relatively slight, but never exaggerated, hypertension, who have been singularly free from past infections and who often give a history of coronary occlusion in several members of their family.

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## THE RED CELL SEDIMENTATION TIME IN CORONARY OCCLUSION\*

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THE sedimentation time is commonly used as an index of the systematic reaction to infection. Up to the present it has been used in infections of all sorts, but particularly in tuberculosis and in gynecological practice. Recently the rate of red cell sedimentation has been stressed as an index of activity in rheumatic fever.

Löhr<sup>1</sup> studied the sedimentation time as an index of the general body reactions during the healing of noninfected wounds and wound-healing following operative procedures which were not made necessary by infection. He studied also the sedimentation time in uncomplicated fractures. He found the sedimentation time definitely lowered after all operative procedures—clean as well as unclean—as well as after noninfected traumatic injuries; the sedimentation time persisted low for many days. These findings have been corroborated by Heusser<sup>2</sup> who attempts to explain postoperative thrombus formation by blood changes of which the increased sedimentation rate is an index.

Since not only infections, but absorptive necrotic processes due to trauma without infection, cause a lowering of the sedimentation time, we became interested in knowing whether cardiac infarction secondary to coronary vessel occlusion would cause similar changes in the sedimentation rate.

In the majority of patients with an acute occlusion of a coronary vessel, systemic manifestations develop quickly. The most commonly noted are fever and leucocytosis. These findings are stressed in the diagnosis of an acute coronary occlusion. They are, however, of relatively short duration, occurring shortly after the insult and persisting only for a relatively short time.

The sedimentation time has been found pathological in chronic infections even though a normal temperature and blood count existed. It was noted after traumatic and postoperative noninfectious states, that the sedimentation time would remain low for many days after the original insult. Westergren<sup>3</sup> states that the sedimentation time decreases a day or two later than the temperature rise in the infectious states, and remains low for two or three weeks after the temperature, pulse and blood counts have returned to normal.

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\*From the Cardiological Department of the Jewish Hospital of Brooklyn.

These data, showing that the lower sedimentation time appears somewhat later than the general signs of activity and persists for an appreciable time after such signs have abated, made us feel that a rapid sedimentation rate, if present, might be used in the diagnosis of a coronary occlusion in such patients as came to us with a history of an attack at a time when the leucocytosis, temperature and other systemic manifestations had abated.

The test in itself has the value of simplicity and lends itself to ordinary bedside practice.

The literature contains many studies on the sedimentation time in infectious conditions, but nothing could be found on the red blood sedimentation rate in coronary occlusion.

#### METHOD

The technic used was that described by Linzenmeier<sup>4</sup>—0.2 c.c. of 5 per cent aqueous solution of sodium citrate was placed in a Linzenmeier tube, 6.5 cm. high with a clear diameter of 0.5 cm. This tube was calibrated at 1 c.c.; 6, 12, 18, and 24 mm. Blood was drawn in a dry hypodermic or tuberculin syringe from the median cubital vein and added up to the 1 c.c. mark; the tube was inverted twice, and then held vertically. The time taken for the blood cells to sediment to the 18 mm. mark was noted.

#### SEDIMENTATION TIME VALUES IN NORMALS AND IN INFECTIOUS DISEASES

Normal values for the sedimentation time by the technic described above have been definitely established. Waugh,<sup>5</sup> Ness<sup>6</sup> and others give the normal sedimentation time to the 24 mm. mark in adult males as 1200 to 1400 minutes; and for adult females 800 to 1000 minutes. Bochner and Wassing<sup>7</sup> give the normal values to the 18 mm. mark as 600 minutes or over. Schmitz and Schmitz<sup>8</sup> report an average sedimentation time in normal adults of about 360 minutes. They suggest that 60 minutes or lower may be regarded as definitely pathological. Baer and Reis<sup>9</sup> feel that a sedimentation time of more than 120 minutes is incompatible with pelvic infection. Polak and Tollefson<sup>10</sup> take 90 minutes as a level, below which they assume the presence of an inflammatory reaction. Numerous other investigators have found figures similar to those given above. One can safely take 60 minutes to 120 minutes as an intermediary zone with values below 60 minutes as definitely abnormal, and values above 120 minutes as not pathological. From the studies of Löhr<sup>1</sup> and Heusser<sup>2</sup> it is seen that while the sedimentation time is not quite as rapid in the noninfectious post-operative or posttraumatic absorptive necrotic processes as in the infections, the same limits of normal may be used.

Since coronary thrombosis is more commonly a disease of advanced years, it is interesting to note the sedimentation time values for

elderly individuals as given by Löw-Beer.<sup>11</sup> This author reports that the sedimentation time increases with advancing years, but that minor infections decrease the sedimentation time more readily in elderly individuals.

While some investigators like Hunt<sup>12</sup> feel that the sedimentation test cannot be relied upon in cases of anemia, others have found that while the sedimentation time is influenced appreciably by variations in the blood cell volume, corrections can be made for such variations. No corrections for cell volume, however, were necessary in this study because anemia was not present in the patients investigated.

Below are presented reports of ten patients who showed the clinical and laboratory data necessary to justify the diagnosis of acute coronary occlusion, in whom the red cell sedimentation rates were studied. No cases are included in this report in which there was any suspicion of the presence of a complicating factor which, like chronic or acute infections, embolic phenomena, etc., might influence the sedimentation rate. Cases I, II, IV, V, VIII and X were uncomplicated. Case III is a diabetic in whom no evidences of infection, either acute or chronic, were noted. Case VI gives a history of having had tuberculosis eighteen years ago. There were no findings indicative of active tuberculosis, either on clinical or on roentgenological examination. Case VII gave a history of having had a gastric ulcer, and having been operated on for a spinal cord tumor eight years previously. Post-mortem examination showed a healed calcified pulmonary tuberculosis and a healed gastric ulcer. Case IX had been operated on; an acute appendicitis was not found and fourteen days after the operative procedure, the sedimentation time was still twenty-five minutes. The operative procedure itself, therefore, cannot be the cause of this finding in this case. Cases IV, V and VII were fatal. Cases IV and VII were necropsied and the diagnosis of an acute coronary occlusion and acute myomalacia cordis confirmed.

#### CASE REPORTS

**CASE I.**—*M. S.* Male; aged 35 years; truck driver. Admitted to the service of Dr. Rosenthal on November 20th, 1930.

Five days prior to admission, while in the subway, patient was suddenly seized with severe substernal pressure, nausea and vomiting. He was treated by an ambulance surgeon and felt more comfortable in a short time; he still complained, however, of a pain of moderate severity in the left chest anteriorly, and a dry cough. These symptoms persisted to the time of admission. *Family History.*—Negative. *Past History.*—Negative. No cardiac or respiratory symptoms prior to the onset of the present illness. Lues denied.

*Examination.*—(Five days after the onset of the attack.) Revealed a muscular, markedly hyposensitive adult male, in fair comfort. The only significant findings were cardiac. The heart percussed 12 cm. from midsternal line in the fifth space, had a rate of 70, and a normal rhythm. The first and second heart sounds were of equal intensity, distant, and of poor quality; A-2 was greater than P-2. No

murmurs or pericardial rub heard. No evidence of syphilis found. No evidence of sclerosis in other peripheral vessel fields. Carotid sinus pressure caused a definite cardiac standstill.

The electrocardiogram shows a regular sinus rhythm, ventricular rate of 65; a right axis deviation with a sharp inversion of the T-1 and a high position of the R-T-1. In the second lead the T-wave is isoelectric. The main deflections are all slurred.

The x-ray film suggested a ventricular aneurysm.

All the laboratory data corroborated the clinical impression of a coronary occlusion.

The laboratory data in this case are presented in Table I.

TABLE I  
CASE I. M. S.

| DAY OF ILLNESS | DATE     | MAXIMUM TEMP.    | MAXIMUM PULSE | BLOOD PRESSURE |     | BLOOD COUNT |       | SEDIMENTATION TIME TO 18 M.M. | REMARKS                       |
|----------------|----------|------------------|---------------|----------------|-----|-------------|-------|-------------------------------|-------------------------------|
|                |          |                  |               | S.             | D.  | W.B.C.      | POLYS |                               |                               |
| 4th            | 11/20/30 | 101 <sup>2</sup> | 70            | 110            | 70  |             |       |                               | Closure on November 16, 1930. |
| 5              | 21       | 101 <sup>4</sup> | 86            |                |     |             |       |                               |                               |
| 6              | 22       | 101 <sup>2</sup> | 88            | 115            | 70  |             |       |                               |                               |
| 7              | 23       | 101 <sup>4</sup> | 88            |                |     | 17,800      | 82%   | 15 min.                       | Hemoglobin                    |
| 8              | 24       | 101 <sup>6</sup> | 68            | 120            | 70  |             |       |                               | 90%.                          |
| 9              | 25       | 100              | 80            | 95             | 40  | 15,600      | 78%   | 17 min.                       | R.B.C.                        |
| 10             | 26       | 99 <sup>6</sup>  | 80            | 90             | 60  |             |       |                               | 5,120,000.                    |
| 11             | 27       | 99 <sup>2</sup>  | 88            |                |     | 8,200       | 64%   | 22 min.                       | Blood Wassermann negative.    |
| 12             | 28       | 99 <sup>2</sup>  | 76            | 105            | 70  |             |       |                               | Blood Kahn                    |
| 13             | 29       | 99 <sup>2</sup>  | 96            | 100            | 60  |             |       |                               | negative.                     |
| 14             | 30       | 99 <sup>4</sup>  | 86            |                |     |             |       |                               | Urine negative.               |
| 15             | 12/ 1/30 | 99 <sup>8</sup>  | 72            |                |     | 7,600       | 77%   | 45 min.                       |                               |
| 16             | 2        | 99 <sup>6</sup>  | 86            |                |     |             |       |                               |                               |
| 17             | 3        | 99               | 80            | 100            | 65  | 8,200       | 66%   | 60 min.                       |                               |
| 18             | 4        | 99               | 80            |                |     |             |       |                               |                               |
| 19             | 5        | 99 <sup>2</sup>  | 72            |                |     |             |       |                               |                               |
| 20             | 6        | 99 <sup>6</sup>  | 86            | 100            | 65  | 9,600       | 71%   | 60 min.                       |                               |
| 21             | 7        | 99 <sup>4</sup>  | 86            |                |     |             |       |                               |                               |
| 22             | 8        | 99 <sup>2</sup>  | 80            | 85             | 50  |             |       |                               |                               |
| 23             | 9        | 99 <sup>6</sup>  | 80            |                |     |             |       |                               |                               |
| 24             | 10       | 99 <sup>2</sup>  | 78            |                |     |             |       | 80 min.                       |                               |
| 25             | 11       | 99 <sup>6</sup>  | 78            | 120            | 80  |             |       |                               |                               |
| 26             | 12       | 99               | 70            |                |     |             |       |                               |                               |
| 27             | 13       | 99 <sup>8</sup>  | 70            |                |     |             |       |                               |                               |
| 28             | 14       | 99               | 68            |                |     |             |       |                               |                               |
| 29             | 15       | 98 <sup>8</sup>  | 68            |                |     |             |       |                               |                               |
| 30             | 16       | 98 <sup>8</sup>  | 70            | 125            | 80  |             |       |                               |                               |
|                | 2/19/31  |                  |               | 170            | 110 |             |       |                               |                               |
|                | 21       |                  | 85            |                |     |             |       | 150 min.                      |                               |

CASE II. A. J. L. Male; aged 60 years; plumber. Admitted to the service of Dr. Shookhoff on November 13, 1930.

For a year prior to admission the patient had typical attacks of angina of effort, and dizziness. These increased in frequency. The day before admission the patient had a very severe attack of precordial pain radiating to the left arm, which persisted for thirty-six hours and which was not relieved by nitroglycerine or by morphine, gr. ss. Patient had a marked pallor and was covered with a cold perspiration.

*Family History.*—Wife had two miscarriages and three children died in early childhood; otherwise negative.

*Past History.*—Lead poisoning with neuritis, thirty years ago. Neuritis of the right arm two years ago. Chronic bronchitis for years. Hypertension for years.

*Examination.*—Revealed an ashen gray facies and an expression of severe pain. The significant findings were cardiac. The heart percussed enlarged to the left; apical impulse neither seen nor felt; pericardial rub audible; a systolic blow over the aortic area and a loud systolic murmur at the apex, transmitted to the axilla, were heard. The first sound was not audible. Carotid sinus pressure caused a definite slowing of the cardiac rate. Liver palpable two fingers below the costal margin and tender. Congestion râles at the base of both lungs. Definite thickening of the walls of the temporal and radial vessels were noted and eye-ground examination showed a definite sclerosis of the retinal vessels. There were no evidences of disturbed kidney function.

The electrocardiogram shows a regular sinus rhythm, ventricular rate of 100. T inverted in all leads. Left axis deviation. Electrocardiograms taken before this attack show a regular sinus rhythm; left axis deviation; no T- or R-T wave abnormalities.

The laboratory data in this case are presented in Table II.

TABLE II  
CASE II. A. J. L.

| DAY<br>OF<br>ILL-<br>NESS | DATE     | MAXI-<br>MUM<br>TEMP.                            | MAXI-<br>MUM<br>PULSE | BLOOD<br>PRESSURE |     | BLOOD<br>COUNT |       | SEDIMENTA-<br>TION TIME<br>TO 18 M.M. | REMARKS   |
|---------------------------|----------|--|-----------------------|-------------------|-----|----------------|-------|---------------------------------------|---|
|                           |          |  |                       | S.                | D.  | W.B.C.         | POLYS |                                       |   |
|                           | 11/11/30 |  |                       | 190               | 100 | (Seen at home) |       |                                       |   |
| 1st                       | 12       |  |                       |                   |     |                |       |                                       | Closure on<br>November 12,<br>1930.<br>R.B.C.<br>5,300,000.<br>Blood Wasser-<br>mann nega-<br>tive.<br>Blood Kahn<br>negative.<br>Urine negative. |
| 2                         | 13       | 100  | 110                   | 140               | 105 | 20,600         | 90%   | 100 min.                              |   |
| 3                         | 14       | 101 <sup>s</sup>                                 | 104                   | 135               | 95  |                |       |                                       |   |
| 4                         | 15       | 102 <sup>s</sup>                                 | 102                   | 110               | 75  |                |       |                                       |   |
| 5                         | 16       | 100 <sup>s</sup>                                 | 98                    | 130               | 85  | 13,100         | 79%   | 13 min.                               |   |
| 6                         | 17       | 101  | 94                    | 125               | 90  |                |       |                                       |   |
| 7                         | 18       | 100 <sup>s</sup>                                 | 92                    | 120               | 80  | 10,500         | 77%   | 18 min.                               |   |
| 8                         | 19       | 100 <sup>s</sup>                                 | 82                    | 130               | 85  |                |       |                                       |   |
| 9                         | 20       | 100  | 88                    | 130               | 80  |                |       |                                       |   |
| 10                        | 21       | 99   | 86                    |                   |     |                |       |                                       |   |
| 11                        | 22       | 99 <sup>s</sup>                                  | 88                    | 125               | 80  |                |       |                                       |   |
| 12                        | 23       | 99 <sup>s</sup>                                  | 90                    |                   |     | 12,800         | 84%   | 41 min.                               |   |
| 13                        | 24       | 99 <sup>s</sup>                                  | 80                    | 130               | 70  |                |       |                                       |   |
| 14                        | 25       | 99 <sup>s</sup>                                  | 90                    | 125               | 80  |                |       | 28 min.                               |   |
| 15                        | 26       | 99 <sup>s</sup>                                  | 90                    |                   |     |                |       |                                       |   |
| 16                        | 27       | 99 <sup>s</sup>                                  | 88                    | 130               | 80  | 9,600          | 78%   | 27 min.                               |   |
| 17                        | 28       | 99 <sup>s</sup>                                  | 88                    |                   |     |                |       |                                       |   |
| 18                        | 29       | 99 <sup>s</sup>                                  | 88                    | 120               | 90  | 8,300          | 78%   | 43 min.                               |   |
| 19                        | 30       | 99 <sup>s</sup>                                  | 78                    |                   |     |                |       |                                       |   |
| 20                        | 12/ 1/30 | 99 <sup>s</sup>                                  | 96                    |                   |     |                |       |                                       |   |
| 21                        | 2        | 99 <sup>s</sup>                                  | 90                    | 125               | 90  |                |       |                                       |   |
| 22                        | 3        | 100 <sup>s</sup>                                 | 84                    |                   |     |                |       |                                       |   |
| 23                        | 4        | 98 <sup>s</sup>                                  | 86                    |                   |     |                |       | 60 min.                               |   |
|                           | 2/26/31  |  |                       |                   |     |                |       | 125 min.                              |   |
|                           | 4/11/31  | (Admitted to Beekman St. Hosp.<br>Mar. 5, 1931.) |                       |                   |     |                |       | 48 min.                               |   |

NOTE.—Sedimentation Time on Feb. 26, was 125 min. In March, patient had another occlusion; was treated at the Beekman St. Hospital for three weeks, and the sedimentation of 48 min. was taken after he left the Beekman St. Hospital.

CASE III. J. G. Male; aged 49 years; clothing merchant. Admitted to the service of Dr. Rabinowitz on April 1, 1931.

Four days prior to admission the patient developed severe pain in the substernal region, the precordium and both shoulders which persisted to the time of admission.

*Family History.*—Negative.

*Past History.*—Diabetes mellitus of moderate severity and of several years duration. No previous effort syndrome. Nothing suggestive of lues.

*Examination.*—Revealed a somewhat dyspneic individual in moderate distress. Heart rate 115, regular. Heart sounds distant, and of poor quality. First sound barely audible. Carotid sinus pressure causes almost a complete standstill. Râles at both bases and the liver edge just barely palpable. Clinical impression—coronary thrombosis.

The electrocardiogram shows a regular sinus rhythm, ventricular rate of 115. The P-R interval is 0.22 seconds. There is a high take-off of the T-wave and a high position of the R-T interval in the first and second leads. T-3 is sharply inverted.

The laboratory data in this case are presented in Table III.

TABLE III  
CASE III. J. G.

| DAY<br>OF<br>ILL-<br>NESS | DATE    | MAXI-<br>MUM<br>TEMP. | MAXI-<br>MUM<br>PULSE | BLOOD<br>PRESSURE |    | BLOOD<br>COUNT |       | SEDIMENTA-<br>TION TIME<br>TO 18 M.M. | REMARKS       |
|---------------------------|---------|-----------------------|-----------------------|-------------------|----|----------------|-------|---------------------------------------|---------------|
|                           |         |                       |                       | S.                | D. | W.B.C.         | POLYS |                                       |               |
| 4th                       | 4/ 1/31 | 101                   | 122                   | 95                | 65 | 10,500         | 81%   |                                       | Closure on    |
| 5                         | 2       | 101 <sup>6</sup>      | 112                   | 125               | 70 |                |       | 25 min.                               | March 28,     |
| 6                         | 3       | 100 <sup>6</sup>      | 110                   | 100               | 72 |                |       |                                       | 1931.         |
| 7                         | 4       | 100 <sup>4</sup>      | 98                    | 100               | 60 |                |       | 18 min.                               | Hemoglobin    |
| 8                         | 5       | 100 <sup>6</sup>      | 90                    | 112               | 78 |                |       |                                       | 85%.          |
| 9                         | 6       | 99 <sup>6</sup>       | 88                    | 120               | 80 |                |       | 18 min.                               | R.B.C.        |
| 10                        | 7       | 99 <sup>6</sup>       | 88                    | 105               | 65 |                |       |                                       | 4,700,000.    |
| 11                        | 8       | 99 <sup>2</sup>       | 80                    |                   |    | 11,500         | 67%   |                                       | Blood Wasser- |
| 12                        | 9       | 99 <sup>4</sup>       | 96                    | 105               | 63 |                |       |                                       | mann nega-    |
| 13                        | 10      | 99                    | 82                    | 105               | 60 |                |       |                                       | tive.         |
| 14                        | 11      | 99                    | 80                    |                   |    |                |       |                                       | Blood Kahn    |
| 15                        | 12      | 99 <sup>8</sup>       | 82                    |                   |    |                |       |                                       | negative.     |
| 16                        | 13      | 99 <sup>2</sup>       | 80                    | 108               | 63 |                |       |                                       | Uranalysis:   |
| 17                        | 14      | 99 <sup>6</sup>       | 78                    |                   |    |                |       | 25 min.                               | Sugar 6.5%    |
| 18                        | 15      | 99 <sup>2</sup>       | 88                    | 110               | 70 |                |       |                                       | to 0          |
| 19                        | 16      | 99 <sup>8</sup>       | 88                    | 105               | 65 |                |       |                                       | (4/11/31);    |
| 20                        | 17      | 99                    | 84                    | 110               | 65 |                |       |                                       | acetone plus; |
| 21                        | 18      | 99                    | 86                    |                   |    |                |       |                                       | diacetic acid |
| 22                        | 19      | 98 <sup>6</sup>       | 86                    |                   |    |                |       |                                       | plus; (nega-  |
| 23                        | 20      | 99 <sup>4</sup>       | 80                    | 90                | 60 |                |       |                                       | tive after    |
| 24                        | 21      | 98 <sup>6</sup>       | 88                    |                   |    |                |       |                                       | 4/11/31);     |
| 31                        | 28      |                       |                       |                   |    |                |       | 30 min.                               | albumin plus; |
|                           | 5/22/31 |                       |                       |                   |    |                |       | 85 min.                               | blood sugar   |
|                           |         |                       |                       |                   |    |                |       |                                       | 300 to 187.   |

CASE IV. J. L. Male; 67 years of age; steward. Admitted to the service of Dr. Alex Louria on January 3, 1931.

Eight months prior to admission the patient was suddenly seized with intense pain in the precordium that radiated down the mesial aspect of both arms to the finger tips; associated with nausea and vomiting. Symptoms lasted forty-eight hours and the patient was in bed for a week. Following this he had transient attacks of precordial pain about every three weeks. The day before admission, while sitting in a chair, the patient had an attack similar to the initial one and vomited six to eight times. Morphine relieved the pain only partly.

*Family History.*—Negative.

*Past History.*—Steward on ship to Porto Rico. Had typhoid, malaria. Nothing suggestive of lues.

*Examination.*—Showed a markedly dyspneic cyanotic elderly male. The important findings were cardiac. The heart percussed enlarged to the left. The apical

impulse was not visible or palpable. Heart sounds barely audible, of poor quality, but regular. A-2 greater than P-2. Marked pericardial friction rub over the apex.

The patient died thirteen days after admission. Autopsy showed a recent thrombosis of the left coronary artery with its resultant myomalacia cordis.

The electrocardiogram shows a regular sinus rhythm, ventricular rate of 95. In leads one and two the R-T interval comes off about the middle of the descending limb of the S. T-wave is very low. All the main deflections are slurred and the QRS intervals are widened. Left axis deviation is present and there are definite evidences of an intraventricular conduction disturbance.

The laboratory data in this case are presented in Table IV.

TABLE IV  
CASE IV. J. L.

| DAY OF ILLNESS | DATE   | MAXIMUM TEMP.    | MAXIMUM PULSE | BLOOD PRESSURE |    | BLOOD COUNT |       | SEDIMENTATION TIME TO 18 M.M. | REMARKS                     |
|----------------|--------|------------------|---------------|----------------|----|-------------|-------|-------------------------------|-----------------------------|
|                |        |                  |               | S.             | D. | W.B.C.      | POLYS |                               |                             |
| 2nd            | 1/3/31 | 101              | 110           |                |    |             |       |                               |                             |
| 3              | 4      | 102              | 128           | 100            | 70 | 17,200      | 81%   | 20 min.                       | Closure on January 2, 1931. |
| 4              | 5      | 102              | 110           |                |    |             |       |                               | Hemoglobin                  |
| 5              | 6      | 101              | 108           | 94             | 70 |             |       |                               | 80%.                        |
| 6              | 7      | 102              | 102           | 100            | 70 |             |       |                               | R.B.C.                      |
| 7              | 8      | 101 <sup>2</sup> | 100           |                |    |             |       |                               | 5,480,000.                  |
| 8              | 9      | 101 <sup>6</sup> | 96            | 100            | 70 |             |       |                               | Urine negative.             |
| 9              | 10     | 100 <sup>8</sup> | 100           |                |    |             |       |                               |                             |
| 10             | 11     | 101 <sup>2</sup> | 112           |                |    |             |       |                               |                             |
| 11             | 12     | 102              | 110           | 108            | 70 |             |       |                               |                             |
| 12             | 13     | 100 <sup>2</sup> | 104           | 100            | 80 |             |       |                               |                             |
| 13             | 14     | 100 <sup>6</sup> | 106           |                |    |             |       |                               |                             |
| 14             | 15     | 100 <sup>4</sup> | 108           |                |    |             |       |                               |                             |
| 15             | 16     |                  |               |                |    |             |       |                               | Died.                       |

CASE V. A. L. B. Female; aged 65 years; housewife. Admitted to the service of Dr. Shookhoff on December 3, 1930.

On December 1, 1930, patient got out of bed to close a window, was suddenly seized with weakness, severe precordial pain, nausea and vomiting. These symptoms persisted to the time of admission.

TABLE V  
CASE V. A. L. B.

| DAY OF ILLNESS | DATE    | MAXIMUM TEMP.    | MAXIMUM PULSE | BLOOD PRESSURE |    | BLOOD COUNT |       | SEDIMENTATION TIME TO 18 M.M. | REMARKS                                       |
|----------------|---------|------------------|---------------|----------------|----|-------------|-------|-------------------------------|---|
|                |         |                  |               | S.             | D. | W.B.C.      | POLYS |                               |   |
| 3rd            | 12/3/30 | 101 <sup>2</sup> | 120           |                |    | 18,800      | 90    | 55 min.                       | Closure on December 1, 1930.                  |
| 4              | 4       | 100 <sup>4</sup> | 122           |                |    |             |       |                               | Died on December 5, 1930.                     |
| 5              | 5       | 99 <sup>6</sup>  | 130           | 110            | 70 |             |       |                               | Blood Wassermann negative.                    |
|                |         |                  |               |                |    |             |       |                               | Blood Kahn negative.                          |
|                |         |                  |               |                |    |             |       |                               | Urine—  |
|                |         |                  |               |                |    |             |       |                               | albumin very faint trace; otherwise negative. |

NOTE.—Blood pressure before attack usually 160/100.

*Family History.*—Father died of a stroke at the age of 64 years. Five children, living and well.

*Past History.*—Typhoid at the age of sixteen. Treated for hypertension with hypertensive anginal attacks for years. Breast abscess at the age of 56 years. Otherwise negative.

*Examination.*—Revealed an elderly woman in moderate pain; somewhat anxious; slightly dyspneic; extremely nauseated. The cardiac findings were as follows: rate 120; rhythm regular, with occasional extrasystoles; basilar vessel line widened to the left and left ventricle not enlarged to percussion; sounds of poor quality, especially the first sound which was barely audible; pericardial friction rub heard. No pulmonary signs. No dependent edema. Sclerosis of retinal vessels.

The patient died suddenly on her third day in the hospital. Autopsy consent was not obtained.

The electrocardiogram shows a regular sinus rhythm with a ventricular rate of 120; T-1 inverted. The R-T interval in the second lead comes off from the middle part of the descending limb of the R-2 and the T-wave is inverted. S-3 is the main deflection. All main deflections are slightly slurred and the QRS intervals are widened, indicating a partial intraventricular conduction disturbance. Occasional ventricular extrasystoles are observed. Electrocardiogram taken some time previous to this attack shows a left axis deviation; no abnormal R-T or T-wave changes; occasional extrasystoles.

The laboratory data in this case are presented in Table V.

CASE VI. A. S. Male; aged 42 years; gasoline dealer. Admitted to the service of Dr. Shookhoff on April 29, 1931.

Patient was well until April 23, 1931, when he was suddenly seized with dizziness and took to bed. He had vague sternal distress but no real pain. No vomiting. No loss of consciousness. No headache or visual disturbance. On April 28th, patient suddenly became pulseless and very pale. Skin was covered with cold perspiration and he became extremely anxious. Hospitalization was advised.

*Family History.*—Unimportant; four children, living and well.

TABLE VI  
CASE VI. A. S.

| DAY<br>OF<br>ILL-<br>NESS | DATE    | MAXI-<br>MUM<br>TEMP. | MAXI-<br>MUM<br>PULSE | BLOOD<br>PRESSURE |    | BLOOD<br>COUNT |       | SEDIMENTA-<br>TION TIME<br>TO 18 M.M. | REMARKS  |
|---------------------------|---------|-----------------------|-----------------------|-------------------|----|----------------|-------|---------------------------------------|--|
|                           |         |                       |                       | S.                | D. | W.B.C.         | POLYS |                                       |  |
| 2nd                       | 4/29/31 | 99 <sup>2</sup>       | 84                    | 130               | 80 |                |       | 270 min.                              | Coronary<br>closure on<br>4/28/31.<br>Hemoglobin<br>90%.<br>R.B.C.<br>4,700,000.<br>Blood Wasser-<br>mann nega-<br>tive.<br>Blood Kahn<br>negative.<br>Urine negative. |
| 3                         | 30      | 99 <sup>4</sup>       | 108                   |                   |    | 16,800         | 69%   |                                       |  |
| 4                         | 5/ 1/31 | 99 <sup>8</sup>       | 128                   |                   |    |                |       | 135 min.                              |  |
| 5                         | 2       | 100 <sup>4</sup>      | 116                   |                   |    |                |       |                                       |  |
| 6                         | 3       | 99 <sup>8</sup>       | 104                   | 120               | 80 | 15,800         | 66%   | 65 min.                               |  |
| 7                         | 4       | 99 <sup>4</sup>       | 104                   | 110               | 70 |                |       |                                       |  |
| 8                         | 5       | 99 <sup>2</sup>       | 96                    |                   |    | 11,100         | 55%   | 60 min.                               |  |
| 9                         | 6       | 99 <sup>6</sup>       | 80                    | 120               | 80 |                |       |                                       |  |
| 10                        | 7       | 99 <sup>4</sup>       | 78                    |                   |    |                |       |                                       |  |
| 11                        | 8       | 99 <sup>6</sup>       | 78                    |                   |    | 10,700         | 63%   | 49 min.                               |  |
| 12                        | 9       | 99 <sup>6</sup>       | 82                    |                   |    |                |       |                                       |  |
| 13                        | 10      | 99 <sup>6</sup>       | 84                    |                   |    |                |       |                                       |  |
| 14                        | 11      | 99 <sup>2</sup>       | 86                    | 115               | 80 | 10,100         | 51%   | 55 min.                               |  |
| 15                        | 12      | 98 <sup>8</sup>       | 84                    |                   |    |                |       |                                       |  |
| 16                        | 13      | 98 <sup>8</sup>       | 80                    |                   |    |                |       |                                       |  |
| 17                        | 14      | 98 <sup>8</sup>       | 84                    |                   |    | 9,850          | 51%   | 60 min.                               |  |
| 18                        | 15      | 99 <sup>2</sup>       | 86                    |                   |    |                |       |                                       |  |
| 19                        | 16      | 98 <sup>8</sup>       | 76                    |                   |    |                |       |                                       |  |
| 20                        | 17      | 99 <sup>2</sup>       | 80                    |                   |    |                |       |                                       |  |
| 21                        | 18      | 99                    | 82                    |                   |    | 8,500          | 58%   | 90 min.                               |  |





One week before admission the patient had a second attack of substernal pressure, choking and vomiting; worse than the first attack, and lasting two days; a third attack occurred the day before admission and was the worst of the three.

*Family History.*—Mother died at the age of 68 years of "apoplexy"; one brother died at the age of 36 years of "Bright's Disease."

*Past History.*—Heavy smoker. Dry cough for fifteen years; spinal cord tumor removed eight years ago; operated on for perforated gastric ulcer seven years ago.

*Examination.*—Showed a hyposensitive male in moderate distress; dyspneic; slightly cyanotic. The heart sounds were weak, regular. No adventitious sounds were made out. The lungs showed many basal râles but there was no dependent edema elsewhere. Diagnosis of coronary occlusion was made. The patient died suddenly on his fourth day in the hospital.

Post-mortem examination showed left coronary thrombosis; adhesive pericarditis; myomalacia and myofibrosis cordis with mural thrombosis; healed apical tuberculosis with calcification; healed perforated gastric ulcer.

The electrocardiogram shows a regular sinus rhythm, ventricular rate of 100; T-1 isoelectric; T-2 and T-3 inverted; left axis deviation.

The laboratory data in this case are presented in Table VII.

CASE VIII. M. O. Male; aged 52 years; grocery clerk. Admitted to the service of Dr. Blatteis on May 14, 1931.

On May 12, 1931, the patient suddenly developed severe precordial pain, chilliness and numbness of both hands. The pain became agonizing, radiated down the inner border of the left arm, and the patient became short of breath. Similar but less severe attacks occurred two and three years ago. Was told he had a hypertension four years ago. Shortness of breath on exertion for many years.

*Family History.*—Unimportant.

*Past History.*—Unimportant.

*Examination.*—Showed a plethoric elderly male with an anxious expression; slight cyanosis and dyspnea. Heart rate 130, regular. Sounds barely audible. Cardiac borders difficult to percuss (chest emphysematous). A-2 greater than P-2. A loud friction rub was audible in the fourth interspace to the left of the sternum. There were coarse râles at the right lung base and the liver percussed slightly enlarged, but there was no pretibial edema.

TABLE VIII  
CASE VIII. M. O.

| DAY<br>OF<br>ILL-<br>NESS | DATE    | MAXI-<br>MUM<br>TEMP. | MAXI-<br>MUM<br>PULSE | BLOOD<br>PRESSURE |    | BLOOD<br>COUNT |       | SEDIMENTA-<br>TION TIME<br>TO 18 M.M. | REMARKS  |
|---------------------------|---------|-----------------------|-----------------------|-------------------|----|----------------|-------|---------------------------------------|--|
|                           |         |                       |                       | S.                | D. | W.B.C.         | POLYS |                                       |  |
| 3rd                       | 5/14/31 | 102 <sup>4</sup>      | 132                   | 128               | 96 | 13,400         | 81%   | 75 min.                               | Closure on May 12, 1931. Hemoglobin 82%. R.B.C. 4,800,000. Blood Wassermann negative. Blood Kahn negative. Urine—Trace of albumin. |
| 4                         | 15      | 103                   | 128                   | 114               | 88 |                |       |                                       |  |
| 5                         | 16      | 102 <sup>4</sup>      | 120                   | 124               | 98 | 12,350         | 87%   | 16 min.                               |  |
| 6                         | 17      | 102                   | 116                   | 128               | 96 |                |       |                                       |  |
| 7                         | 18      | 102                   | 100                   | 122               | 86 |                |       |                                       |  |
| 8                         | 19      | 100 <sup>6</sup>      | 100                   | 124               | 86 | 16,600         | 78%   | 26 min.                               |  |
| 9                         | 20      | 100 <sup>4</sup>      | 100                   |                   |    |                |       |                                       |  |
| 10                        | 21      | 100                   | 100                   | 112               | 74 |                |       |                                       |  |
| 11                        | 22      | 100                   | 98                    |                   |    |                |       |                                       |  |
| 12                        | 23      | 102                   | 114                   | 108               | 72 |                |       |                                       |  |
| 13                        | 24      | 100 <sup>4</sup>      | 120                   |                   |    |                |       |                                       |  |
| 14                        | 25      | 100                   | 120                   | 106               | 72 | 9,400          | 65%   |                                       |  |
| 15                        | 26      | 99 <sup>8</sup>       | 110                   | 114               | 76 |                |       |                                       |  |
| 16                        | 27      | 99 <sup>8</sup>       | 110                   | 117               | 80 | 11,000         | 75%   |                                       |  |
| 17                        | 28      | 99 <sup>4</sup>       | 100                   | 98                | 66 |                |       |                                       |  |
| 24                        | 6/ 4/31 |                       |                       |                   |    |                |       | 50 min.<br>120 min.                   |  |

The electrocardiogram shows definite evidences of an acute myocardial involvement.

On May 26, patient again experienced an attack of precordial pain. On auscultation a friction rub again was heard. He is still in the hospital at this writing but is free of symptoms. On June 4, 1930, the sedimentation time was 120 minutes.

The laboratory findings are presented in Table VIII.

CASE IX. W. S. Male; aged 45 years; clothing operator. Admitted to the surgical service on May 5, 1931.

Two days before admission he developed severe umbilical cramps that radiated to the back; associated with nausea, but no vomiting. Temperature 100-101. No right lower quadrant pain. Symptoms persisted to the time of admission.

*Family History.*—Negative.

*Past History.*—Negative. Venereal disease denied.

*Examination.*—Showed a plethoric adult male, with a flushed facies. Patient was of the hyposensitive type. No dyspnea or cyanosis. Pupils regular, equal and reactive. Throat injected moderately. Lungs negative. Heart—rate regular, 100. No enlargement. Sounds of good quality; A-2 greater than P-2. No murmurs. Abdomen—Negative. No definite tenderness, rebound tenderness or rigidity. Extremities negative.

The diagnosis of acute appendicitis was made and appendectomy performed on May 6, 1931. At operation the appendix did not look inflamed. The pathological report was chronic catarrhal appendicitis. The next day the patient developed a rapid, irregular pulse and an electrocardiogram was taken.

The electrocardiogram shows an auricular flutter with a ventricular rate of 188 and a 2:1 block.

The clinical course and electrocardiographic findings made the probable diagnosis coronary thrombosis.

Electrocardiogram taken on May 24, shows that the auricular tachycardia is no longer present; a regular sinus rhythm with a ventricular rate of 97 is now present. The P-R interval in the second lead is 0.26 seconds (partial A-V block) and there is a left axis deviation. Definite evidence of myocardial damage is present.

The laboratory findings are presented in Table IX.

TABLE IX  
CASE IX. W. S.

| DAY<br>OF<br>ILL-<br>NESS | DATE    | MAXI-<br>MUM<br>TEMP. | MAXI-<br>MUM<br>PULSE | BLOOD<br>PRESSURE |    | BLOOD<br>COUNT |       | SEDIMENTA-<br>TION TIME<br>TO 18 M.M. | REMARKS   |
|---------------------------|---------|-----------------------|-----------------------|-------------------|----|----------------|-------|---------------------------------------|---|
|                           |         |                       |                       | S.                | D. | W.B.C.         | POLYS |                                       |   |
| 3rd                       | 5/ 5/31 | 101 <sup>8</sup>      | 120                   | 112               | 80 | 14,200         | 81%   |                                       | May 6, 1931,<br>appendectomy.<br>Closure on May<br>3, 1931 (?).<br>Urine—Neg-<br>ative. |
| 4                         | 6       | 102 <sup>4</sup>      | 126                   |                   |    |                |       |                                       |   |
| 5                         | 7       | 102 <sup>8</sup>      | 130                   | 146               | 82 |                |       |                                       |   |
| 6                         | 8       | 102 <sup>4</sup>      | 120                   |                   |    |                |       |                                       |   |
| 7                         | 9       | 101 <sup>8</sup>      | 104                   |                   |    |                |       |                                       |   |
| 8                         | 10      | 100 <sup>4</sup>      | 100                   |                   |    |                |       |                                       |   |
| 9                         | 11      | 100 <sup>6</sup>      | 88                    |                   |    |                |       |                                       |   |
| 10                        | 12      | 101 <sup>8</sup>      | 100                   |                   |    |                |       |                                       |   |
| 11                        | 13      | 102                   | 92                    |                   |    |                |       |                                       |   |
| 12                        | 14      | 102                   | 92                    |                   |    | 9,000          | 69%   |                                       |   |
| 13                        | 15      | 101 <sup>6</sup>      | 100                   |                   |    |                |       |                                       |   |
| 14                        | 16      | 102 <sup>4</sup>      | 84                    |                   |    |                |       |                                       |   |
| 15                        | 17      | 102 <sup>4</sup>      | 80                    |                   |    |                |       |                                       |   |
| 16                        | 18      | 102 <sup>8</sup>      | 66                    |                   |    |                |       |                                       |   |
| 17                        | 19      | 102                   | 72                    | 120               | 80 |                |       | 25 min.                               |   |

NOTE.—Temperature returned to normal on May 27. The sedimentation rate at that time was 65 minutes.

CASE X. L. A. Aged 63 years. Patient of Dr. Shookhoff.

This patient has had a hypertension for many years. One year ago he had an attack of pain in the chest with radiation down the arms and a diagnosis of a coronary occlusion was then made.

*Family History.*—Father and mother died of unknown cause. Had one brother who had a hypertension and coronary disease. Family and past history otherwise negative.

Patient had been moderately well, experiencing no symptoms up to the onset of this present attack, when on April 30, 1931, he developed a severe pain in the chest, radiating to the back and down both arms—pain was vise-like, excruciating, and required two half-grains of morphine sulphate to relieve him.

*Examination.*—Revealed an elderly man, brownish greyish facies and slightly cyanosed. Blood pressure 100/80 mm. Many congestive râles at both bases. Heart—aortic configuration, left ventricular enlargement. Heart sounds were distant; first sound was barely audible; carotid sinus pressure caused a complete cessation of cardiac activity for a short time. The cardiac rate was about 120. The abdomen was very slightly distended; liver was palpable two fingers below the costal margin and tender. No edema.

One day after the attack, April 31, 1931, the leucocyte count was 12,500 white cells with 70 per cent Polys., and the sedimentation time was 170 minutes.

This patient was treated at home and could not be followed properly. However, a sedimentation time taken on May 6 (six days after onset of attack), was 30 minutes.

He subsequently developed a cerebral insult causing a left hemiplegia and no further studies were made.

## RESULTS

The sedimentation times ranged from 270 minutes to 13 minutes. Sixty minutes was taken arbitrarily as the point below which the sedimentation time was interpreted as definitely pathological. The value fell below sixty minutes in all the cases.

In Cases II, VI, VIII and X, the first sedimentation rate estimations were made on the day following the attack and, while the temperature and blood picture were already abnormal, the sedimentation readings were still normal. They became more rapid subsequently. In Cases I, III, IV, V and IX, the first sedimentation test was not made until several days after the attack and the figures were all below normal. In Case VII the sedimentation time of 37 minutes was obtained on the third day of illness, but there had been recent previous attacks. These cases seem to show that the sedimentation time becomes pathological later in the disease than the temperature and blood count. The lowest level was reached as early as the fifth day following the closure in Cases II and VIII, and as late as the eleventh day in Case VI. Thereafter, in all cases the values increased toward normal. Tables I, II, III, VI, VIII and IX show that the low sedimentation time outlasted, by an appreciable number of days the return of the temperature and blood count to normal. Only one sedimentation time each was obtained in Cases IV, V and VII; these patients died. The sedimentation times in these latter three cases were

all low. The results indicate that the sedimentation time is definitely shortened in cases of acute coronary occlusion. The cases presented in this study had no known infections or other complications that might have caused the abnormal sedimentation times. The more rapid rate occurs relatively late in the disease; it persists, however, longer than does the fever and leucocytosis. This determination, therefore, may be valuable in cases appearing for examination a number of days after an attack and presenting a normal temperature and blood count.

From this study we are unable to state whether or not the extent of the drop in the sedimentation rate is proportional to the extent of tissue destruction in the heart. In studies on the sedimentation rate in other conditions, a relationship between the rate of sedimentation time and extent and severity of lesion has been sought. Thus, in a study of 250 gynecological cases, Benischek and Douglas<sup>13</sup> concluded that the speed of sedimentation was directly proportional to the extent and severity of the pelvic inflammation. Tappan and Faget<sup>14</sup> investigated 234 cases with pulmonary tuberculosis and found the sedimentation rate to be proportional to the extent of anatomical involvement and to be an index of activity. The same relationship between extent of lesion and sedimentation rate may be found in coronary occlusion when a large enough number of cases have been studied and checked up by post-mortem findings.

It seems justifiable to assume that while the sedimentation time is abnormally low, active changes are taking place in the heart muscle. We feel that this test offers a valuable index of the repair process and that the infarctive reaction cannot be regarded as having subsided until the sedimentation rate has risen to at least above the sixty minute level. Polak and Tollefson<sup>10</sup> state that when the sedimentation time is rapid in gynecological cases, they have always found, by operation or by further observation of the clinical course, existing pathological conditions to account for the low determination.

The rapidity with which the value returns to normal is in all probability related to the speed of healing. For this reason repeated determinations of the sedimentation rate may aid materially in prognosis and treatment. In the light of the results presented even in this small series of cases, it appears advisable to keep a patient with a coronary occlusion in bed for at least as long as the sedimentation time still suggests active myocardial changes, i.e., as long as it is below sixty minutes.

We hope that this brief report will encourage further study of the sedimentation time in this type of disease, with a view to establishing this simple procedure as an aid to diagnosis, prognosis and treatment of acute coronary occlusion.

## SUMMARY AND CONCLUSIONS

The red cell sedimentation time was studied in ten patients who presented sufficient clinical symptoms and laboratory data to make probable the diagnosis of an acute coronary occlusion. Two of three patients who died were necropsied and coronary occlusion with an acute myomalacia was found.

It was observed in these cases that the sedimentation time was definitely shortened, that this change appeared later in the disease than did the fever and leucocytosis, and persisted for some time after the temperature and blood count had returned to normal. The persistence of this rapid sedimentation rate beyond the time when the temperature and blood changes had disappeared made it, for us, a better index of the progress of the healing of an acute myomalacia due to a coronary occlusion than the temperature and leucocytosis.

NOTE: We wish to thank Drs. Rosenthal, Rabinowitz, Louria, and Blatteis for their kind cooperation in allowing us to use their clinical material.

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# CARDIOVASCULAR DISEASE

## A REPORT OF 398 CASES COMING TO NECROPSY\*

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IN THE four years from 1927 to 1930, out of 2344 autopsies at the Cincinnati General Hospital the primary cause of death in 398, or 17 per cent, of the cases was breakdown of the cardiovascular system. In this group of "cardiovascular deaths" all cerebral vascular accidents are included but arteriosclerotic kidney cases are omitted because the connection between the renal lesion and the death of the patient is often indefinite. In all of these cases the diagnoses have been carefully controlled by microscopic examination and so possess more value than would the clinical, or even the gross pathological diagnoses alone. These 398 cases have been analyzed in regard to (1) type of cardiovascular disease (classification of the American Heart Association), (2) inactivity period before death, (3) age at death, (4) race, (5) cardiac hypertrophy.

The percentage of autopsies in which cardiovascular breakdown was the primary cause of death varied little from year to year during the period. In 1927 it was sixteen; 1928, nineteen; 1929, seventeen; 1930, sixteen.

### TYPE OF CARDIOVASCULAR DISEASE

As to the type of cardiovascular disease at death the etiological classification of the American Heart Association has been followed, with the omission of the diagnoses: thyroid, toxic, neurosis (cardiac) and trauma. In the beginning of this study the syphilitic and the arteriosclerotic heart cases were entirely separated, but this was not found to be practical since a large number of those cases in which death was primarily due to syphilitic heart disease, also showed minor evidence of arteriosclerosis, and some cases in which death was primarily due to arteriosclerotic heart disease, also presented minor evidence of syphilis. For this reason it was necessary to make certain changes in classification. Of the 398 cardiovascular deaths, 164 or 41 per cent resulted from arteriosclerotic heart disease, and 50 or 13 per cent from arteriosclerotic heart disease with minor evidence of syphilis. Combining these two figures there were 214 deaths or 54 per cent caused by arteriosclerotic heart disease. Fifty-five deaths, or 14 per cent of the 398 cardiovascular

\*From the Department of Pathology, University of Cincinnati, and Cincinnati General Hospital.

deaths, resulted from syphilitic heart disease, while 34, or 9 per cent resulted from syphilitic heart disease with minor evidence of arteriosclerosis. Combining these last two figures there were 89, or 23 per cent, which were caused by syphilitic heart disease. The remainder of the 398 deaths are classified as follows: rheumatic heart disease 11, or 3 per cent; acute and subacute bacterial endocarditis 36, or 9 per cent; unclassified 8, or 2 per cent; congenital heart anomalies 14, or 4 per cent, and pericarditis, acute and chronic 13, or 3 per cent. In the last group it was necessary to depart from the etiological classification and pass over to an anatomical classification. (See Table I.)

TABLE I  
TYPES OF CARDIOVASCULAR DISEASE WITH PERCENTAGES

|  |     |
|--|-----|
| A. Arteriosclerotic heart disease                            | 41% |
| B. Arteriosclerotic heart disease + syphilitic heart disease | 13% |
| C. Syphilitic heart disease                                  | 14% |
| D. Syphilitic heart disease + arteriosclerotic heart disease | 9%  |
| E. Rheumatic heart disease                                   | 3%  |
| F. Acute and subacute bacterial endocarditis                 | 9%  |
| G. Unclassified  | 2%  |
| H. Congenital heart anomalies                                | 4%  |
| I. Acute and chronic pericarditis.                           | 3%  |

Of the arteriosclerotic cardiovascular deaths, 65, or 30 per cent, were due to cerebral vascular accidents, while only 12, or 13 per cent, of the syphilitic cardiovascular deaths resulted from such accidents.

In this entire series of cardiovascular deaths, 35 per cent of the cases showed some evidence of syphilis, while only 13 per cent of routine autopsies at the Cincinnati General Hospital, over the same period of time, presented evidence of syphilis.

#### PHYSICAL INACTIVITY PERIOD FOR VARIOUS TYPES OF HEART DISEASE

By the phrase "Physical Inactivity Period" is meant the length of time that elapses between the onset of cardiovascular symptoms of such severity that the patient is no longer able to maintain his normal activity and the time of death. Here the cases were divided into the same etiological groups as before. For the arteriosclerotic group the inactivity period averaged 10.1 months, while for the arteriosclerotic cases with minor evidence of syphilis it averaged 14.0 months. The inactivity period average for the entire arteriosclerotic group was 11.3 months. From the above figures it appears that the persons with arteriosclerosis and syphilis have a longer inactivity period than those with arteriosclerosis alone. The reason for this is that in the arteriosclerotic cases with minor evidence of syphilis there were a few patients that lived over seven years, and these few were sufficient to raise the average inactivity period for this group. The patients with syphilitic heart disease had an inactivity period of 6.4 months, while those with syphilitic heart disease



with minor evidence of arteriosclerosis had an inactivity period of 12.8 months. The inactivity period average for the entire syphilitic group was only 8.7 months, as compared with 11.3 months for the arteriosclerotic group. In the syphilitic heart disease group the same paradox appears as in the arteriosclerotic group, and the same explanation holds true here, only the syphilitic heart disease group was smaller so the difference caused by a few cases living over seven years was even greater. The inactivity period for the rheumatic heart disease group was 6.6 months while for the acute and subacute bacterial endocarditis group it was only 2.5 months. The inactivity period for the pericarditis heart disease group as well as the congenital heart anomaly group was not determined. The brevity of the inactivity period for these cases may appear discouraging, even alarming, but it is neces-

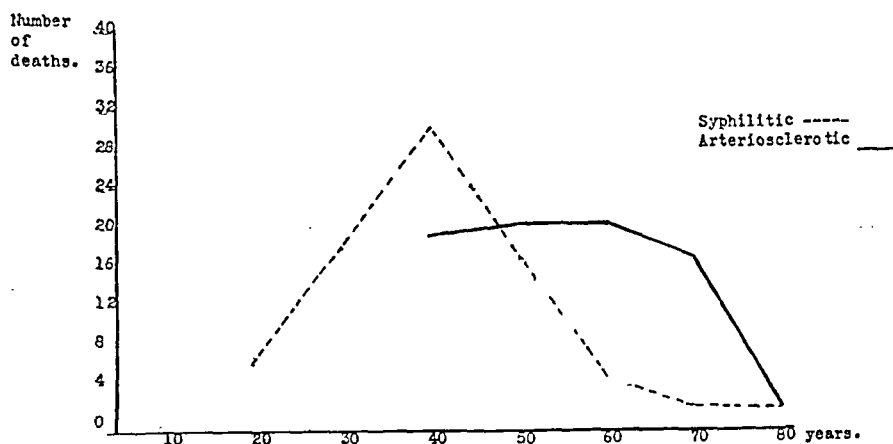


Fig. 1.—Age at death in 80 arteriosclerotic and 80 syphilitic cardiovascular deaths.

sary to make note of the fact that the patients represented here came largely from the indigent and underprivileged ranks of society, and included a number of negroes.

#### AGE AT DEATH

The average age at death of the patients dying of arteriosclerotic disease was 59.4 years, while of those dying of arteriosclerotic disease but also showing minor evidence of syphilis it was 57 years. Combining these two figures this represents an average of 59.1 years for the entire arteriosclerotic heart disease group. The average age at death of the patients dying of syphilitic heart disease was 45 years, while of those dying of syphilitic heart disease with minor evidence of arteriosclerosis it was 46.6 years. This represents an average of 45.6 years for the entire syphilitic group as compared with 59.1 for the entire arteriosclerotic group. The average age at death for the rheumatic heart disease group was 26.5 years, while that for the bacterial heart disease group was 38.4 years. In the remaining types the number of cases was not considered large enough to warrant averaging the age at death.

In 80 unselected cases of arteriosclerotic cardiovascular deaths and a similar number of syphilitic cardiovascular deaths, the age at death was plotted against the number of cases dying at that age. The results are striking. In the syphilitic heart disease group there is a very definite peak at 40 years and then a rapid decline, while in the arteriosclerotic heart disease group there is a rather broad plateau extending over the fifth, sixth and seventh decades. (See Fig. 1.)

#### RACE

In the routine autopsies at the Cincinnati General Hospital from 1927 to 1930 56 per cent of the patients were white and 44 per cent black. In the series of patients dying of arteriosclerotic cardiovascular disease, 38 per cent were black and 62 per cent were white, while of those dying of syphilitic cardiovascular disease, 80 per cent were black and only 20 per cent were white. The above figures suggest that syphilitic cardiovascular disease is approximately four times as common in the black as in the white race.

#### CARDIAC HYPERTROPHY

An attempt was made to appraise some of the factors causing cardiac hypertrophy. In the arteriosclerotic heart disease group there was no constant correlation between the amount of hypertrophy and the condition of the macroscopic coronary vessels, but there was a fairly constant correlation between the length of the physical inactivity period and amount of hypertrophy; in other words, the longer the inactivity the greater the hypertrophy regardless of the condition of the macroscopic coronaries. In the syphilitic cardiovascular group the average heart weight in cases with aneurysms was less than the average heart weight in those cases without aneurysms; that is, aneurysms as such do not lead to cardiac hypertrophy. The heart weight in those cases with adhesive pericarditis was greater than that in any other group.

#### SUMMARY

A statistical study, of 398 autopsied cases dying primarily of a breakdown of the cardiovascular system, is presented, concerning type of cardiovascular disease, physical inactivity period before death, age at death, race and cardiac hypertrophy.

# VENTRICULAR PAROXYSMAL TACHYCARDIA: REPORT OF A CASE IN A PREGNANT GIRL OF SIXTEEN YEARS WITH AN APPARENTLY NORMAL HEART\*

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WE ARE reporting this single case of ventricular tachycardia because of the several unusual and interesting features which it presented. These were: (1) the youth of the patient (sixteen years); (2) the almost continuous presence of the disturbance; (3) the possible relationship of pregnancy; (4) its improvement under digitalis and its abolition by quinidine; (5) the absence of any demonstrable cardiac disease; and (6) the fact that cesarean section was performed uneventfully during this disturbance of the cardiac action.

## CASE REPORT

The patient, a young, colored girl of sixteen, illegitimately pregnant, came to the Pre-natal Clinic of the Philadelphia General Hospital in the seventh month of gestation. At this clinic, a rapid and somewhat irregular heart action was discovered, and she was referred to us for study.

There were no cardiovascular symptoms whatsoever, not even consciousness of the paroxysms of rapid heart action. Nor were there any symptoms referable to the gastrointestinal, genitourinary, respiratory, or nervous systems. The family history was entirely negative. The past medical history, likewise, revealed nothing of importance. There had been infrequent, mild sore throats, but nothing further suggestive of rheumatic fever; she was not even aware of having had any of the ordinary diseases of childhood.

The physical examination was largely negative. Except for being under normal height (she was five feet tall and weighed 102 pounds) she appeared normally developed and nourished. The head, teeth and tonsils revealed nothing abnormal. There was slight fullness in the region of the thyroid gland. The lungs were entirely normal, both clinically and by x-ray.

The heart was not definitely enlarged by percussion. The left border measured 10.0 cm. to the left of the midsternal line in the fifth interspace and the right 2.5 cm. in the fourth interspace; the retrosternal dullness in the second interspace was 5.0 cm. By teleroentgenogram, the total diameter of the heart measured only 11.2 cm. with a maximum intrathoracic diameter of 22.8 cm. The heart sounds were not remarkable and there were no murmurs. On our first examination, the heart was found most of the time to be beating regularly at a rate of 150 per minute with an occasional brief period of a slower rate. The mechanism was shown by electrocardiograph to be ventricular paroxysmal tachycardia with brief intervals of sinus rhythm interspersed. The blood pressure was 130/80 mm. The abdomen showed nothing of note except the enlarged uterus, and the extremities were not abnormal.

\*From the Division of Cardiology of the Philadelphia General Hospital and The Robinette Foundation for the Study of Cardiovascular Diseases of the University of Pennsylvania.

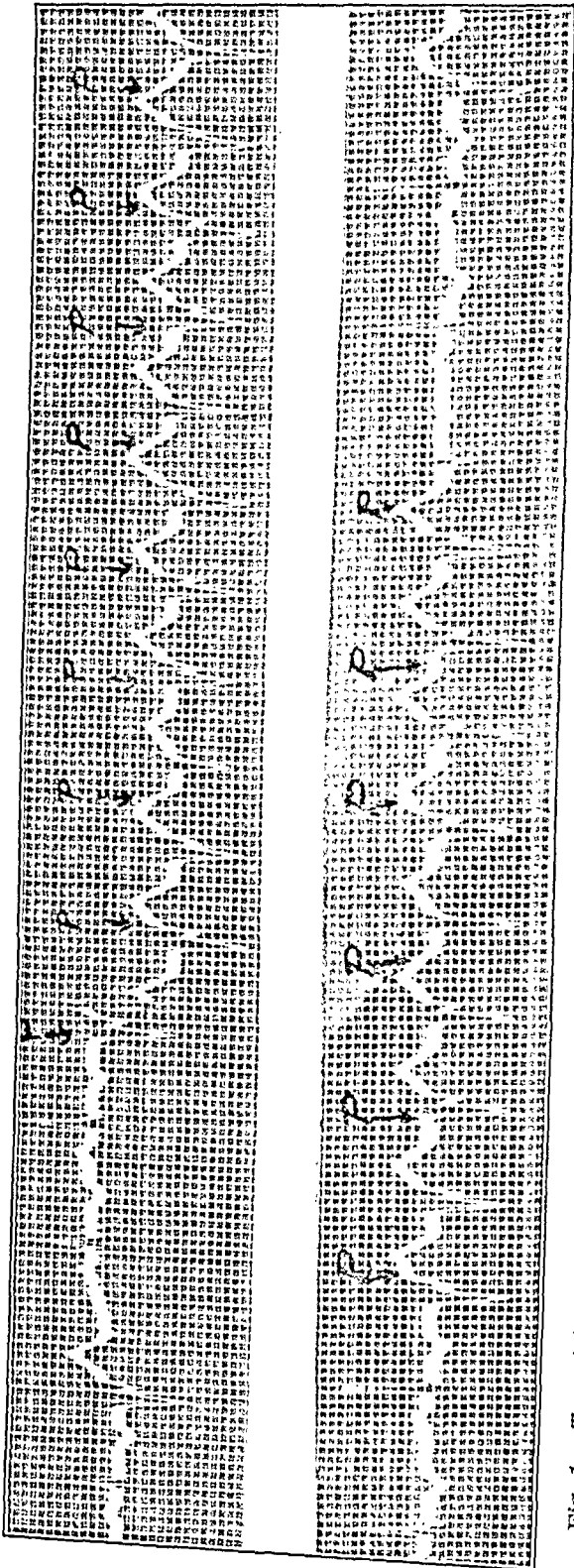


Fig. 1.—Two strips, both Lead II, show the auricular and ventricular dissociation. The P-waves are plainly seen, occurring at a slower rate than the ventricular impulses. Isolated extrasystoles are also seen. In the second strip, the first beat of a paroxysm is coupled to a preceding normal beat by the same interval as in isolated extrasystole.

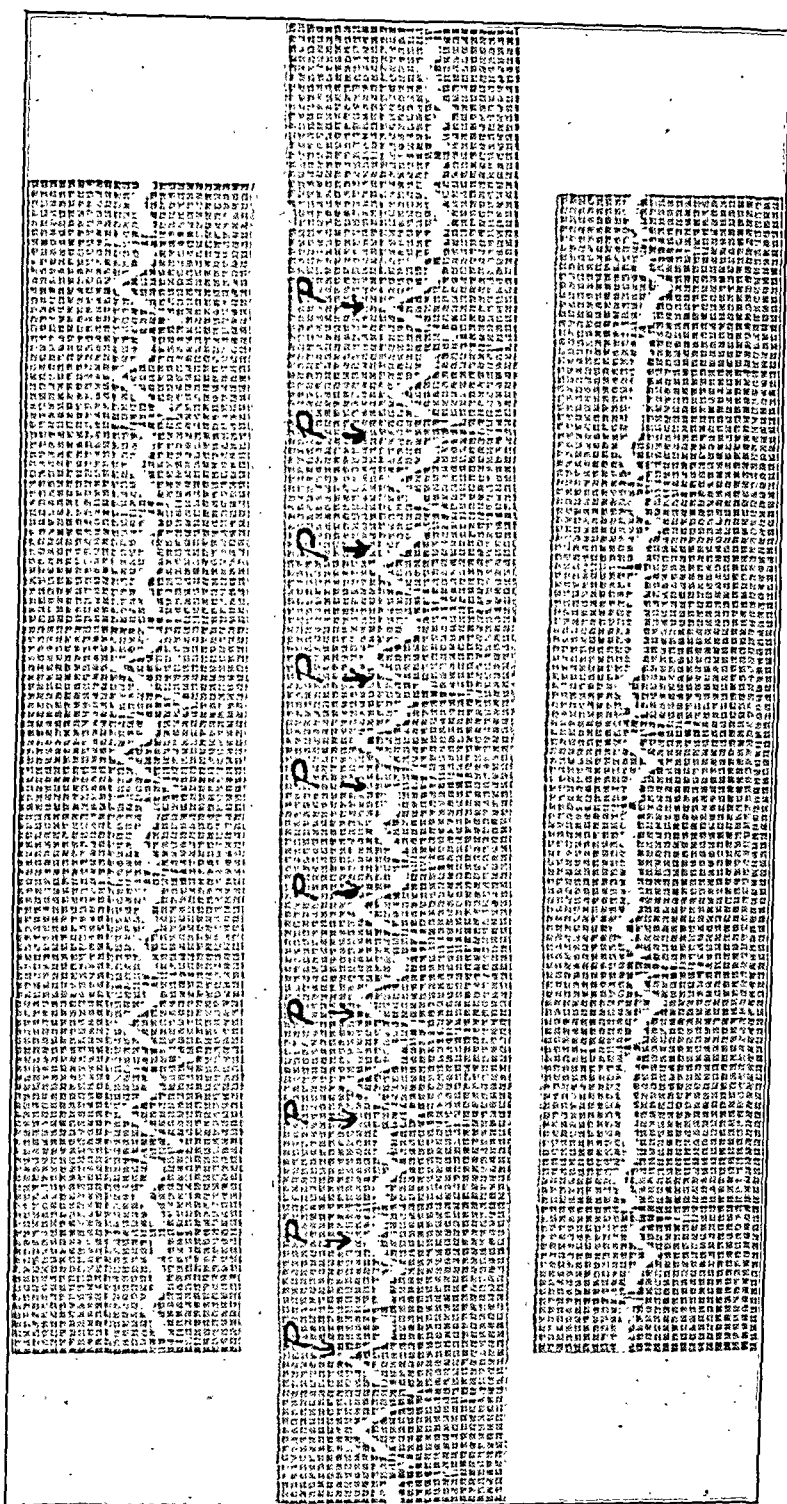


Fig. 2.—The three customary leads. One short paroxysm of tachycardia is shown. At no place in the tracing are more than two normal beats seen in sequence. In Lead III, a bigeminal rhythm is seen. This tracing was obtained after treatment had been instituted.

The urine, blood count and blood chemistry were normal, and the Wassermann test was negative.

*Electrocardiograms.*—In Figs. 1 and 2 (both obtained after one week of hospitalization) the tachycardia is seen to be composed of widened, aberrantly shaped ventricular complexes that are entirely independent of, and more rapid than, the auricular waves. Moreover, there are isolated, premature beats, almost certainly ventricular in origin, which are identical in shape with the complexes making up the paroxysm. The latter beats are sometimes accurately coupled to preceding normal beats, and frequently the first beat of the paroxysm is coupled to a preceding normal beat by the identical interval.

Fig. 3 is shown to illustrate the almost continuous nature of the paroxysmal disturbance as it existed before treatment was instituted, the tachycardia being

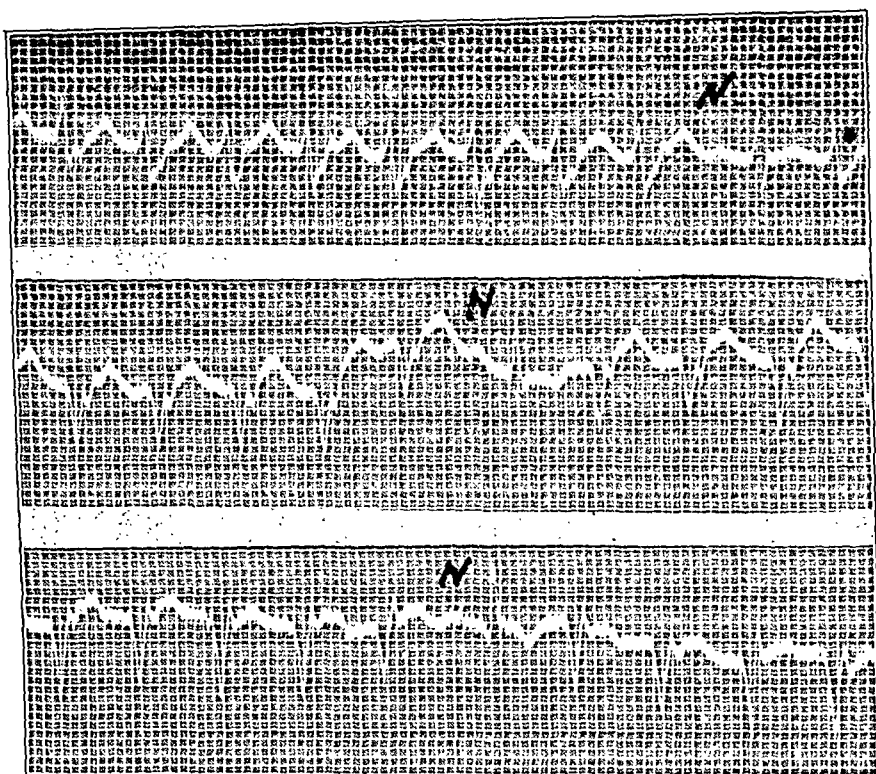


Fig. 3.—The three customary leads as they were observed before treatment. Tachycardia was present almost constantly. In each lead shown, only one normal supra-ventricular complex is seen. The T-waves of the normal complexes are inverted in Leads II and III.

interrupted only occasionally by single normal cycles. Until treatment was begun, the periods of tachycardia far exceeded the periods of normal rhythm.

Fig. 4 shows the electrocardiogram after the tachycardia had been abolished by quinidine.

#### *The Effect of Drugs, Vagal Pressure and Exercise*

*Digitalis.*—Four and one-third ( $4\frac{1}{3}$ ) drams of the tincture of digitalis administered in a period of three days caused no change. Later, she was put on one dram of the tincture daily until signs of toxicity, in the form of nausea, headache and vomiting, appeared on the fifteenth day. On the fifth day of this régime and at various times afterward during the drug's administration normal rhythm appeared, but this was not firmly established; for such factors as exercise and emotional disturbance caused an immediate return of the tachycardia. More-

over, with the appearance of toxic digitalis effects, the tachycardia reappeared as the predominant mechanism. The most that can be said therefore is that digitalis in therapeutic amounts discouraged the tachycardia.

*Quinidine.*—The effectiveness of quinidine in controlling ventricular tachycardia has been well established.<sup>18, 5, 7, 13, 8, 3</sup> While our patient was having almost continuous paroxysmal tachycardia, the administration of quinidine sulphate was begun. After a total of thirty-five grains had been given in three days, a constant normal rhythm was restored with a ventricular rate of eighty-eight (88). The drug was then omitted and after three days paroxysms of tachycardia returned and persisted almost continuously during its omission. This procedure was repeated a number of times and always the arrhythmia disappeared on as much as five

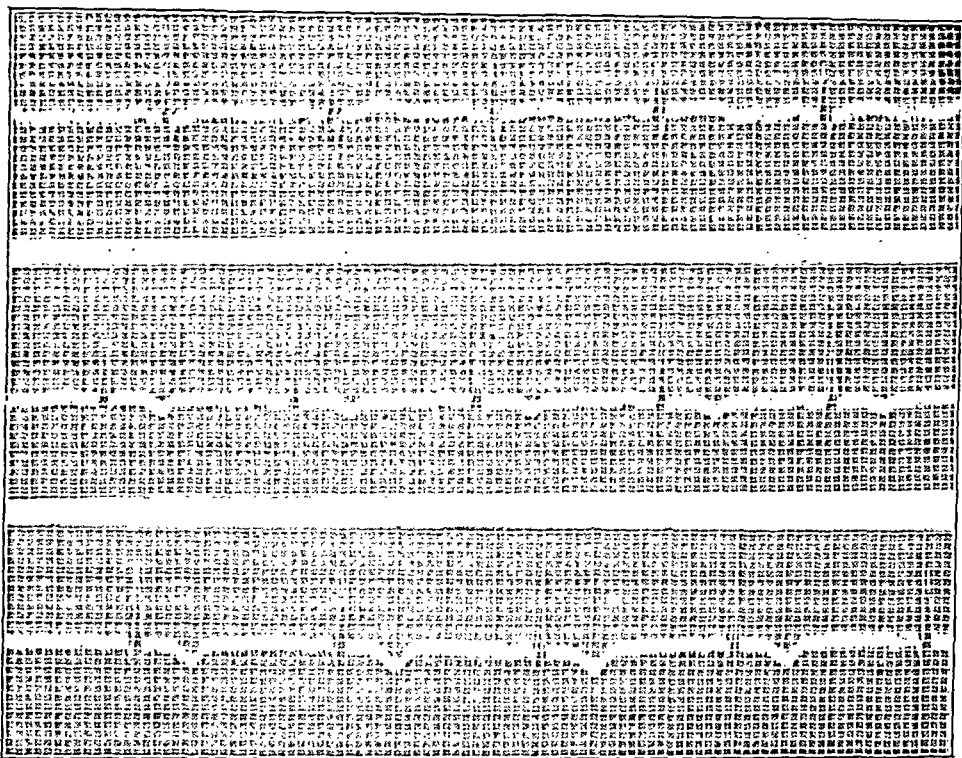


Fig. 4.—The three usual leads obtained after normal rhythm had been established under quinidine. The T-waves in Leads III and III are inverted.

grains of quinidine sulphate four times a day (frequently smaller amounts sufficed), and invariably returned when the drug was discontinued. The abolition of the arrhythmia under this drug was moreover apparently complete in that emotion, exercise, and atropine did not cause its reappearance. Under the circumstances of this case, we feared to give much quinidine for its possible untoward effect on the uterine muscle. These fears were justified inasmuch as signs of a threatened abortion did develop while the patient was receiving only nine grains of quinidine sulphate daily. After this episode, quinidine was not given again until after delivery.

*Digitalis and Quinidine Combined.*—A combination of 15 minims of the tincture of digitalis and 3 grains of quinidine sulphate three times daily restored and maintained a normal rhythm during its administration. In view of the response to each drug separately, it seems not improbable that the effects noted were really due to quinidine and not to the digitalis which was given with it.

*Exercise, Vagal Pressure, and Atropine.*—With the tachycardia almost continuous as it was before treatment was begun, we could see no effect of exercise. When the tachycardia had disappeared under digitalis, it promptly reappeared under the influence of exertion. While the tachycardia was absent under the influence of quinidine, we were unable to make it reappear by exercise or even atropine. Digital pressure over the vagus nerve in the neck had no demonstrable effect upon the ectopic rhythm.

We attempt to draw no conclusions from these observations. We had hoped to make more thorough observations after the puerperium was completed, but were unable to induce the patient to return for further studies after her discharge from the hospital.

#### Clinical Course

As the end of term approached, it was felt that cesarean section was the method of delivery that offered the fewest risks. This was accomplished successfully and uneventfully under spinal anesthesia by Dr. John McGlinn.

Fear of the possible depressing effects of quinidine on the respiratory center of the child led us to allow the patient to go into the operation with the tachycardia in full swing. Just before operation the tachycardia and periods of normal rhythm were intermingled as we had so often observed them. During the operation the tachycardia became entirely continuous with a rate of 150.

After delivery the abnormal rhythm continued to be present just as it had been during pregnancy and continued to be easily controllable by quinidine. Since her discharge we have been unable to make further observations, but have learned from a physician who has seen her from time to time that the tachycardia as shown by electrocardiograms is still present more than a year after our original observations were made. The last electrocardiogram that we ourselves made was obtained three months after delivery.

#### DISCUSSION

*Incidence and Diagnosis of Ventricular Tachycardia.*—This disturbance of the cardiac rhythm has always been regarded as rare. Its diagnostic features were somewhat confused until 1920, when Robinson and Herrmann<sup>14</sup> reported four cases and laid down certain criteria for a positive diagnosis. Submitting all the reported cases to examination, they accepted only eighteen as definite examples of ventricular tachycardia. Their criteria have been generally accepted, and since the publication of their paper there have been added a number of cases which complied with these. Recently Strauss<sup>16</sup> has reviewed all the reported cases and accepted sixty-five as being definite examples of ventricular paroxysmal tachycardia.

We doubt if the condition is as rare as the scarcity of reported cases would indicate. We have encountered thirteen instances among 16,000 electrocardiograms secured from 6,500 different patients, which fulfilled the criteria of Robinson and Herrmann.<sup>14</sup> It is probable that others have had a similar experience.

We have often wondered if A-V dissociation with a ventricular rate more rapid than the auricular might not under certain circumstances simulate a tachycardia of ventricular rather than of junctional origin. The circumstances under which this might occur would be those of an



accompanying widening of the ventricular complexes. There is evidence that junctional impulses may occasionally result in aberrant ventricular complexes,<sup>4</sup> the aberration at times even reaching the stage of widening.<sup>20</sup> If this did occur and the ventricular impulses were independent of, and more rapid than, auricular beats, ventricular tachycardia rather than the real condition might be diagnosed. However, when isolated extrasystoles are present and coupled to preceding normal complexes as they were in our case, a ventricular origin seems unquestionable.

*Age of Onset.*—While the number of reported cases of ventricular tachycardia is rapidly accumulating, few instances have been reported in young persons. Strauss<sup>16</sup> in his recent analysis found only three examples in persons less than twenty years of age. We have been able to find six reported examples among the reports of Wolferth and McMillan,<sup>10</sup> Jones and White,<sup>5</sup> Gilchrist,<sup>3</sup> Gallavardin and Veil,<sup>2</sup> and Anderson.<sup>1</sup> The youngest of any of these six cases was seventeen years of age. The age of our patient, sixteen years, is therefore, unusual.

Recently, Moore<sup>11</sup> has reported an interesting disturbance of rhythm in a boy of twelve years as an example of ventricular tachycardia. Study of the published tracings lead us to feel that this diagnosis on the evidence presented is somewhat open to question.

*The Condition of the Heart in Ventricular Tachycardia.*—In most of the reported cases there has been unquestionable evidence of cardiac disease. Levine and Fulton<sup>8</sup> state that ventricular tachycardia may occur on rare occasions in young people in whom there are found no signs of heart disease and in whom the only cardiac symptoms present are those associated with the tachycardia. They cite three examples: one reported by Scott,<sup>15</sup> one by Jones and White,<sup>5</sup> and one of their own.<sup>8</sup> However, Scott's patient was an invalid when she came under observation and, moreover, gave a history of a previous rheumatic infection. The case reported by Jones and White<sup>5</sup> showed definite cardiac enlargement. Levine and Fulton's patient<sup>8</sup> showed no demonstrable cardiac abnormality, but was forty-one years of age. In a report by Gallavardin and Veil,<sup>2</sup> the patient, a boy of seventeen, had no definite cardiac symptoms but the heart was enlarged. The example of ventricular paroxysmal tachycardia recently reported by Anderson<sup>1</sup> occurred in a boy of seventeen years, who showed no evidence whatever of heart disease. It is apparent, therefore, that ventricular tachycardia occurs but rarely in patients who present no demonstrable cardiac damage.

In our case we were unable to find anything by clinical study that could be interpreted as evidence of heart damage. X-ray examination showed the heart was definitely not enlarged, though by percussion it was on the borderline; but in one with the habitus of our patient and

with the addition of a seven months' pregnant uterus, we feel that the percussion measurements could be discounted even without the aid of the x-ray pictures. There is but one finding that leaves any doubt in our mind as to the absence of cardiac damage; this is the presence in the electrocardiograms of inverted T-waves in Leads II and III. We can only say of this finding that we know it can be the result of preceding cardiac damage; on the contrary, we see the change not infrequently in hearts that are considered to be unimpaired.

*The Relation of Ventricular Tachycardia to Pregnancy.*—It is not unusual to encounter extrasystoles during and apparently the result of pregnancy. Paroxysmal tachycardia on the other hand has been infrequently reported.<sup>6, 10, 12, 17, 9</sup> In those cases studied with the electrocardiograph, the origin of the tachycardia has been either auricular or nodal. The case of MacKenzie,<sup>9</sup> studied with the polygraph, was thought to be ventricular.

There is no evidence that establishes pregnancy as the cause of paroxysmal tachycardia of any variety. In most of the reported cases the disturbance had existed as a paroxysmal manifestation before pregnancy had begun. In our case the persistence of the tachycardia after the termination of pregnancy rules out gestation as the cause.

As a complication of labor, paroxysmal tachycardia, especially in diseased hearts, may be a serious matter as some of the reports referred to indicate. In patients whose histories indicate a serious circulatory response to attacks of paroxysmal tachycardia, it may be well at least to consider cesarean section as the method of delivery unless the disturbance is readily controllable. This means of terminating pregnancy was chosen in one of the cases of Meyer, Lackner and Schochet<sup>10</sup> and in our case. In both instances the results were highly satisfactory.

#### SUMMARY

A case of ventricular tachycardia is reported in which the following interesting features are to be noted: (1) the youth of the patient (sixteen years); (2) the absence of any definite evidence of a damaged heart; (3) the occurrence of the disturbance during pregnancy and its failure to disappear upon the termination of gestation; (4) the ready abolition of the tachycardia by quinidine; and (5) the successful and uneventful outcome of a cesarean section performed during the tachycardia.

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## ANOMALOUS PAPILLARY MUSCLE ATTACHED TO PULMONARY VALVE OF HEART\*

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IN 1896, Browicz reviewed the literature on anomalous chordae tendineae and papillary muscles occurring in the heart. He was the first to classify these anomalies and his classification is still the stand-

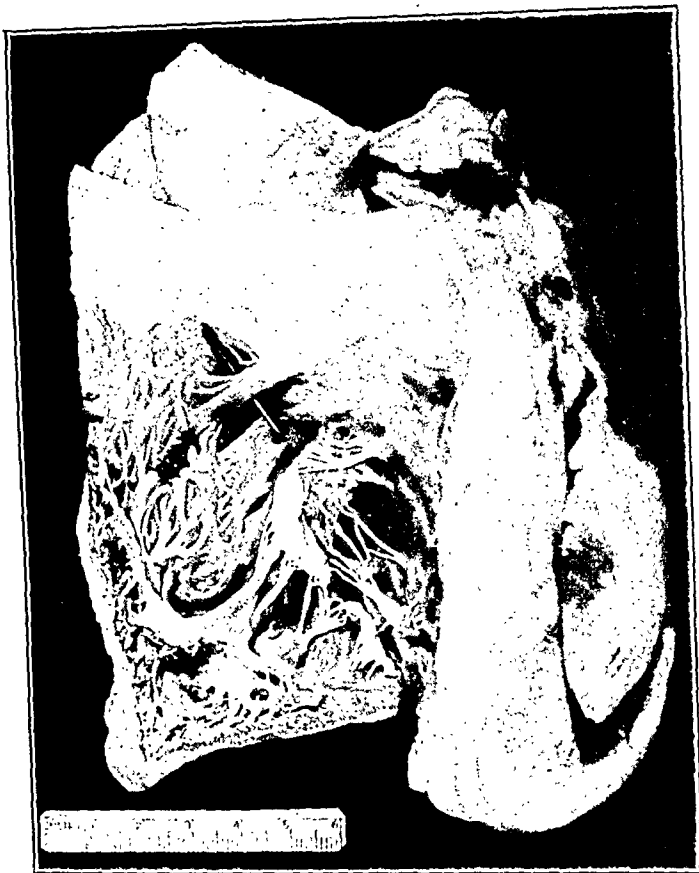


Fig. 1.—Gross appearance of the right ventricle of the heart. An anomalous papillary muscle is inserted into the anterior cusp of the pulmonary valve. The single chorda tendinea may be seen lying between the probe, which passes behind the anomalous papillary muscle and the base of the valvular cusps.

ard. The types are as follows: (1) normal papillary muscles; (2) so-called moderator band, stretching across the cavity of the right ventricle from the base of the anterior papillary muscle to the septum; (3) muscular chords running along the walls, usually of the ventricles, without any connection with valve curtains or trabeculae; (4) chords or

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TABLE I  
REVIEW OF LITERATURE ON ANOMALOUS CHORDAE TENDINEAE AND PAPILLARY MUSCLES

| YEAR | CLASS (BROWICZ) | RE-PORTER                  | CASES | AGE, SEX, YR.          | SITUATION IN HEART                               | ORIGIN  | INSERTION                                | CLINICAL DATA   |
|------|-----------------|----------------------------|-------|------------------------|--|---|--|---|
| 1870 | 4               | Mayne                      | 1     | Not given              | Left ventricle, below aortic valve; 2 chordae    | Not given   | Not given                                | Loud apical systolic murmur                           |
| 1876 | 4               | Cuffer                     | 1     | 35 F                   | Left ventricle                                   | Anterior leaf of mitral valve                                     | Wall of left ventricle below aorta       | Basal murmur; mitral insufficiency                    |
| 1878 | 4               | Archer                     | 1     | Not given              | Across aortic orifice                            | Not given   | Not given                                | Not given   |
| 1879 | 4               | Surbled                    | 1     | 33 F                   | Left ventricle                                   | Anterior papillary muscle   | Behind mitral valve                      | Mitral insufficiency                                  |
| 1879 | 4               | Demange                    | 1     | 70 M                   | Right ventricle, anterior to tricuspid valve     | Wall of right ventricle   | Wall of right ventricle                  | Tricuspid insufficiency                               |
| 1879 | 4               | Veradini                   | 1     | Not given              | Left ventricle, below aortic orifice to chorda   | Wall of left ventricle  | Wall of left ventricle                   | Loud systolic murmur                                  |
| 1882 | 5               | Fowler                     | 1     | 42 M                   | Left ventricle, left auricle                     | Left edge of foramen ovale  | Left auricular appendage                 | Carcinoma of liver; heart negative                    |
| 1884 | 4               | Engel                      | 1     | Not given              | Left ventricle, across aortic orifice            | Wall of left ventricle  | Aortic valve, posterior cusps            | Aortic insufficiency, diastolic murmur                |
| 1892 | 4               | Huchard                    | 1     | 49 M                   | Left ventricle                                   | Wall of left ventricle  | Wall of left ventricle                   | Interstitial nephritis, basal systolic murmur, thrill |
| 1896 | 5-(1)<br>4-(1)  | Turner                     | 2     | Not given              | One in left ventricle; one involving both valves | Near foramen ovale  | Mitral valve                             | Not given   |
| 1896 | 5-(1)<br>4-(2)  | Rolleston                  | 3     | 1 M<br>Not given       | Left ventricle<br>Left ventricle                 | Left auricle<br>Left papillary muscle                             | Left ventricle<br>Right papillary muscle | Not given<br>Not given                                |
| 1896 | 5               | Griffith                   | 1     | Not given<br>Not given | Left ventricle; 2 chordae<br>Left auricle        | Papillary muscles of left ventricle<br>Left side of foramen ovale | Mitral valve<br>Left ventricle           | Not given<br>Not given                                |
| 1896 | 5-(2)           | Bisad-<br>eck and<br>Feigl | 2     | Not given              | Left ventricle                                   | Near foramen ovale  | Left auricular appendage<br>Mitral valve | Not given<br>Not given                                |

bands stretching across any one of the cardiac chambers from a papillary muscle or from one wall to the other, and inserting in a valve (and commonly giving rise to the high-pitched, musical, basal systolic murmur, transmitted upward toward the vessels of the neck and occasionally diastolic in time) and (5) anomalous chords extending from either auricle into the ventricle, originating from the edges of the valve over the foramen ovale and inserted into one of the auriculoventricular valves.

Table I contains a review of the literature on this subject from 1870 to 1931. Papillary muscles of the right ventricle attaching themselves to the pulmonary valve were reported in but 2.2 per cent of the cases found in the literature, and therefore constitute an uncommon cardiac anomaly.

#### REPORT OF CASE

The case to be reported is that of a man, aged sixty-nine years, whose weight was 215 pounds and whose height was 182 cm. The patient died of a disease totally unrelated to the cardiac anomaly, in life made no complaints relative to the heart, and on physical examination revealed no cardiac murmurs.

The heart weighed 400 gm. The foramen ovale was closed. Aside from the condition of the pulmonary valve, and sclerosis, graded 1, of the aortic valve and the anterior leaflet of the mitral valve, the valves and endocardium appeared normal. The right auricle was dilated, graded 2. There was sclerosis of the right coronary artery, graded 2, and of the left coronary artery, graded 3; the lumen of the latter was markedly stenosed. At a distance of 7 cm. from the apex of the right ventricle and 2 cm. mesially to the cut left lateral aspect of the right ventricle, there originated a thick, muscular band distinct from the myocardium (Fig. 1). It extended for a distance of 2.3 cm. and was inserted directly into the base of the anterior cusp of the pulmonary valve. The diameter of this band, at its origin in the wall of the right ventricle, measured 1 cm., whereas its diameter at the point of its insertion into the pulmonary valve was 0.5 cm. One chorda tendinea, measuring 0.8 cm., originated on the left side of this muscular bundle, and was inserted into the myocardium at the base of the line of juncture between the left lateral and anterior cusps of the pulmonary valve. This anomalous papillary muscle is of type 4, as described by Browicz. The presence of one chorda tendinea in this case clearly establishes this muscle bundle as being an anomalous papillary muscle and not an aberrant trabecula corneae. Its congenital origin seems to be clearly established.

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## THE CLINICAL SIGNS OF OCCLUDING THROMBI OF THE LEFT AURICLE\*

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**I**T WAS in 1890 that Von Ziemssen<sup>1</sup> suggested for the first time the possibility of recognizing the clinical manifestations of occluding auricular thrombi. He concluded from a study of three patients, that the presence of an obstructing ball or pedunculated thrombus in the left auricle could be diagnosed on the basis of circumscribed gangrene of the feet, cadaveric coldness and swelling of the lower extremities and absent or diminished arterial pulsations in the larger vessels of the legs. He attributed the latter signs to an extreme diminution of the blood flow from the left ventricle to the periphery by a thrombus superimposed on a pre-existing stenosed and narrowed mitral orifice. This pathological condition he found in all of his three cases. He based the development of gangrene of the feet on a similar mechanism although the possibility of marantic thrombi or emboli to the larger vessels of the legs could not be ruled out.

A few years later, Bozzolo<sup>2</sup> reported the case of a woman, forty-three years of age with mitral stenosis, in whom he established a diagnosis of an occluding thrombus of the left auricle and confirmed the findings at autopsy.

About one month after her recovery from a left hemiplegia, his patient began to complain of severe precordial pains and cough without expectoration. One week later, she experienced pain in her entire left leg and following that, the extremity began to swell and to feel cold and numb. Shortly after, the same signs appeared on the right side. A few days later, the left leg presented a mottled discoloration, livid in color, that extended from a little above the knee to the lower part of the leg.

When examined by Bozzolo, she showed marked cyanosis of the face and lips. Both feet were intensely cyanosed and had a greenish tinge which merged imperceptibly with a lighter area, pinkish in color, near the ankles. One of her legs presented a large necrotic area 3 cm. long and 1 cm. wide on its outer aspect near the lower part of the tibia. Pressure over the popliteal space of that leg was very painful.

The heart rate was fast and irregular. The radial arteries were barely palpable and only the right pulse was present.

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Autopsy revealed a large pedunculated thrombus of the left auricle in addition to the mitral stenosis. The vessels of the extremities were not opened.

In 1909, Battistini<sup>3</sup> diagnosed, during life, "thrombosis" of the left auricle in two patients with mitral stenosis. His first case was a male, forty-six years of age, who complained of coldness in his lower extremities ten days before his admission to the hospital. On examination, his legs showed large scars of a violaceous color without any definite borders. The superficial veins near these areas were distended. The femoral pulses could not be obtained, and the left radials and carotid pulses were not palpable. Unfortunately further details of this case are wanting.

At autopsy this patient revealed a large rounded thrombus of the auricle adherent to the parietal wall and obstructing a stenosed mitral orifice. There were also partial obliterating thrombi in the lumen of the femoral vessels and the popliteal artery.

His second case was a woman of forty-four years with mitral stenosis who shortly before her admission to the hospital complained of severe dyspnea and cyanotic discoloration of both her legs. On examination she showed gangrene of both feet. The right leg was cold and numb and devoid of all sensations. Her radial and carotid pulsations were weak and irregular. She died thirty days after the onset of these signs.

At autopsy, a large thrombus was found attached to the auricular wall by a long pedicle, which permitted it to play freely over the stenosed mitral orifice.

Another case, similar to these, although complicated by subacute bacterial endocarditis was seen by Lutembacher.<sup>4</sup> His patient was a woman twenty-eight years of age with mitral stenosis and a rapid and irregular heart rate who had lost the sight of her right eye. While under observation, she developed a gradual discoloration of her nose which at first was bluish in color and at the end of eight days became black and gangrenous. This dried, and was ready to drop off. Within two weeks several necrotic spots appeared on the face and forearms. Death took place three weeks after the onset of these signs.

At autopsy a ball thrombus was found present in the left auricle in addition to the stenosed mitral orifice.

In a man aged forty-one years, with mitral stenosis and auricular fibrillation, Aubertin and Rime<sup>5</sup> noted the appearance of purpuric spots on the lower extremities and palms of the hands followed within four days by a progressive increase in the discoloration of the last phalanges of the right hand. The oscillometric readings on both arms were only one-half of a division. Gradually the tip of the nose became discolored and cold. Death took place fourteen days after the appear-

ance of these symptoms, and at autopsy a large pedunculated thrombus was found over-riding a stenosed mitral orifice.

This diagnosis was suspected during life, emphasis being placed on the marked hypotension with disappearance of the first heart sound and the progressive asphyxia of the hands, feet and nose with cyanosis, coldness and the diffuse purpuric eruption. Unfortunately no examination was made of the vessels supplying the extremities.

In another patient with azotemia and progressive asphyxia of the extremities who died four days after the onset of these signs, these authors could not obtain a post-mortem examination to confirm their suspicions of an occluding auricular thrombus.

In a woman aged fifty-five years, with mitral stenosis and auricular fibrillation Covey, Crook and Rogers<sup>6</sup> noted the development of sudden pain and bluish discoloration of the entire left leg. Within a few hours, the pain became more severe, and it appeared to them that the presystolic murmur previously present had increased in intensity at the same time. A diagnosis of an occluding auricular thrombus of the ball-valve type was suspected and this was confirmed at autopsy. Permission, however, was not obtained for examination of the femoral artery of the left leg which they believed to have been obstructed by an embolus.

To this series we wish to add three more cases that have been seen by us during the past few years at the Montefiore and Morrisania Hospitals in all of which we suspected the presence of an occluding auricular thrombus from the nature of the physical signs present. Contrary to the beliefs of Welch<sup>7</sup> and Hewitt<sup>8</sup> we feel that such a diagnosis is possible although we would not draw a "clear" distinction between a ball and pedunculated thrombus. The recognition of these clinical signs is of importance for they presage death within a very short time after their appearance.

#### REPORT OF CASES

CASE 1.—F. F., a female, aged 44 years, was admitted to the Montefiore Hospital on Oct. 5, 1926, and died on Oct. 28, 1926. Her chief complaints were dyspnea, weakness, nausea and vomiting.

*Previous Illness.*—The patient became ill for the first time in May, 1917, when she entered the Presbyterian Hospital because of shortness of breath and weakness. She was readmitted to the same institution on four separate occasions within the next few years because of repeated attacks of shortness of breath, palpitation of the heart and swelling of the lower extremities. While there, on September 26, 1926, the tips of all of her toes and all of her fingers were noted to have become uniformly deeply cyanotic and very tender. This condition cleared up somewhat on the following day, but the first and second toes of the right foot remained deeply purple and gangrene set in.

*Physical examination* on admission to the Montefiore Hospital revealed a pale undernourished woman showing marked respiratory difficulty. Her neck veins were distended. The apical impulse of her heart was in the sixth intercostal space in

the left anterior axillary line. There was a marked apical systolic thrill. The first heart sound was almost completely replaced by a loud blowing systolic murmur.  $P_2$  was accentuated. The heart rate was 140, the rhythm irregular and there was a pulse deficit of 28 beats per minute. The blood pressure was approximately 190 mm. of mercury systolic and 90 mm. diastolic. The edge of the liver was palpable in the right iliac fossa. The lower extremities revealed a moderate amount of edema, most of which was localized above the ankle.

The finger tips of both her hands were cyanotic, the purplish discoloration extending as far as the first joint. They all presented on the volar surface, darker, hemorrhagic spots which were extremely tender on pressure. Placing the hand in hot water did not change the color, although pressure on the pad of the distal phalanges caused blanching. The tips of all of her toes were similarly affected but not to as great an extent.

Both radial as well as the posterior tibial and dorsalis pedis arteries were visibly pulsating.

*Course in Hospital.*—On Oct. 8, 1926, two days after admission, she developed numerous red spots in the axillary region. These were irregular in outline, disappeared on pressure, but not with change in position. They increased in number following a thoracentesis of the right chest. Within the next two weeks, the signs of congestive heart failure became more prominent, so that one week prior to her death she showed extensive edema of both her arms and legs as well as marked ascites.

The tips of her toes and fingers turned black and became dry and puckered. There was progressive cyanosis and a darker discoloration of the tip of her nose, although no frank gangrene developed. At no time throughout the period of observation was there noted a fall in blood pressure. A pulse was felt in all of the large peripheral arteries until the day of her death.

An unusual observation was the failure of digitalis to slow the ventricular rate materially even though she received 3 c.c. of the tincture daily.

The patient died in coma, a little more than one month after the onset of these peripheral circulatory changes.

*Autopsy Findings.*—(Only the points of interest are reported here.) The heart was moderately enlarged and roughly globular. It weighed 700 grams. The epicardial surfaces all over were thin, smooth and glistening except for a slight opacity over both auricular appendages and a small milk patch at the upper posterior angle of the right ventricle.

The base of the heart was dilated, the right lateral border of the left auricle forming the upper border of the right side of the heart. The right auricle was markedly enlarged and the auricular appendage was firm. On section, the auricular cavity was dilated while the auricular wall was hypertrophied.

The left auricle was strikingly enlarged. Its capacity was judged to be approximately 300 c.c. It was partly filled with blood. After removing the unclotted blood, a large irregular thrombus, somewhat pyramidal in shape, was seen to extend from the tip of the auricular appendage as far as the orifice of the mitral valve. The thrombus was free except for its attachment to the auricular appendage and could be easily displaced from over the mitral orifice. It measured 10 cm. from tip to tip. It was of a firm consistency, its lower pole hugging the left leaflet of the mitral valve but extending almost across the orifice.

The right ventricular wall measured 5 to 7 mm. in thickness. There was marked dilatation with a slight hypertrophy of the conus of the pulmonary artery.

The pulmonary orifice measured 8 cm. and except for slight thickening of the corpora Arantii, there were no abnormalities.

The left ventricle was dilated and hypertrophied, its wall measuring from 10 to 15 mm. in thickness.

The mitral orifice was irregular in outline but admitted the tips of two fingers. The leaflets were all fused into a continuous and markedly thickened mass of tissue. There was a ridge of soft polypoid vegetations along the lines of closure. The chordae tendineae were all thickened, shortened and hyalinized. The papillary muscles were markedly hypertrophied.

The aortic orifice measured 6 cm. All three leaflets were moderately thickened and shortened, and in part calcified. The sinuses of Valsalva were slightly enlarged. Along the line of closure of all three leaflets, there were continuous ridges of warty vegetations similar to those of the mitral valves.

The coronary arteries were patent throughout.

The aorta and its tributaries showed no abnormalities and there were no thrombi or emboli in the large vessels of the extremities.

The vena cava and its branches contained no thrombi.

CASE 2.—F. S., a married woman, aged 42 years, was admitted to the Montefiore Hospital on Nov. 22, 1929, and died on Nov. 24, 1929. She was first seen in consultation with Dr. C. S. Mirkin in September of that year.

*Previous Illness.*—The patient had been perfectly well until two and a half years before (July, 1927) when she began to complain for the first time of recurrent attacks of palpitation of the heart and shortness of breath on exertion. She was treated with quinidine for several weeks and felt well enough to be up and about until Oct. 14, 1928, when she suffered a left hemiplegia. From this time on she showed auricular fibrillation, and it is stated by her physician that she responded promptly to rapid digitalization, her ventricular rate averaging 70 beats per minute three days later.

She remained in bed for three weeks and recovered almost completely save for numbness of the left hand which still persisted.

With the exception of several attacks of epistaxis, she remained free from symptoms until Sept. 4, 1929. When seen on that day, the patient was vomiting, she was disoriented, her speech was altered, her memory was poor, but she did not present any other neurological manifestations. She recovered from all of these symptoms within one week.

On the night of Nov. 4, 1929, the patient was awakened suddenly by a sharp lancinating pain in the midsternal region. When seen an hour later, she was sitting up in bed breathing with difficulty. The respirations were 34 and labored, the temperature was 101° F. and the heart rate was totally irregular and averaged 180 beats with a deficit of 40 beats per minute. There was a definite wheeze to her respirations. A slight but persistent cough was always accompanied by blood-tinged sputum. On the following morning, she brought up large clots of blood. From then on, the patient's dyspnea increased and her ventricular rate remained at over 100 beats per minute despite the fact that she received 54 c.c. of the tincture of digitalis within twenty days.

Throughout the rest of her period of observation, she complained of periodic seizures of pain over her precordium. These were constricting in type, radiated to the back and then to left side of the neck and ear. Occasionally, the pain would radiate to the inner side of the arm and remain there. More often, a constricting sensation of the left arm above the wrist would be her only symptom. She obtained great relief from small doses of morphine sulphate. With the persistent high ventricular rate which was refractory to large doses of digitalis, signs of congestive heart failure developed very rapidly. The liver became large and tender to pressure, there was swelling of her legs, and the only method of relieving her dyspnea was to have her sit up with her head bent far forward and reclining on her folded arms.

Throughout this time, her mentality was fairly clear. She answered questions rationally but her memory was very poor.

On Nov. 17, 1929, she was suddenly awakened with a severe pain in her right leg and a dull aching pain in her back. At 9 P.M. of that day, examination revealed nothing unusual in that limb except some lack of sensation to the pin-prick test. The right femoral artery was pulsating and there was a visible pulsation in the right dorsalis pedis artery.

On the evening of Nov. 21, 1929, she complained of a persistent severe headache followed by nausea, vomiting, incontinence of feces and of urine, and at one period of the day her eyes were seen to roll to one side, she foamed at the mouth and could not speak. At 4 A.M. of the following morning she was perfectly rational but complained of numbness in both her legs from the hips downward.

When seen at this time, physical examination revealed a slight pitting edema of both lower extremities. There was pulsation in both femoral arteries. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of good quality, the first sound being partly replaced by a loud blowing systolic murmur. The blood pressure was approximately 190 mm. of mercury systolic and 110 mm. diastolic, and it was practically the same on both sides. There was moderate congestion at the bases of both lungs. The liver edge was palpable 8 cm. below the costal margin. The ventricular rate was 185 beats per minute with a pulse deficit of almost 50 beats.

She was seen again on Nov. 22, 1929, when she complained of a very severe pain in the whole of the right leg. At this time the entire limb had a cadaveric appearance with mottling and marmoration of the skin from the hips to the toes. No pulsation was felt in the femoral or the dorsalis pedis arteries. The limb was cold to touch and was covered with a clammy sweat. There were diminished muscular power and loss of sensation on this side.

When reexamined at the hospital, on the afternoon of that day, both legs appeared normal. Although several of our associates were inclined to believe that she had suffered an embolus to the right femoral artery in the morning, they could not explain these signs in the afternoon.

Twelve hours later, the patient was seen in shock. She was conscious but could not talk. Her face had an anxious expression and was of a ghastly color. There was marked distention of her neck veins. The heart rate was very rapid and irregular. The right pulse was not palpable. The left was barely felt. Both of her femoral arteries were now pulseless, and oscillometric readings were not obtainable at any level on either lower extremity.

The oscillometer readings on the upper extremities revealed only slight movements in the left arm but none in the right. The color of the lower half of the body had a post-mortem appearance, pale with mottling and the cyanosis that is usually seen in patients shortly after death. It was cold and clammy to touch. Five minutes after these examinations, complete positive oscillometer readings were obtained on all extremities and there was a return of all pulses to the touch. The color of the skin appeared normal again.

Throughout the rest of this day (Nov. 24, 1929) the patient presented on and off, such symptoms and signs as were described above and at one time, during the absence of all pulsations, short tonic and clonic convulsions were noted in various parts of the body.

The heart sounds, the heart rate and rhythm presented unusual clinical features during this time. When pulsations were not palpable in the peripheral vessels, there was almost complete absence of heart sounds. The rate was extremely rapid averaging 200 beats per minute, but at times on listening over the precordium the heart sounds could barely be heard.

The patient died in coma on the evening of the same day.

*Autopsy Findings.*—The heart was enlarged and weighed 410 grams. The epicardial surfaces all over were smooth and glistening. Both auricles and ventricles were moderately dilated.

In the left auricle, there was found a round, fairly smooth, red, spherical thrombus about 4.5 cm. in diameter. Its lower pole facing the mitral valve was slightly indented into a mould that fitted the orifice very snugly. On section, the thrombus presented a large area of soft spongy grey matter in its interior. There were no other thrombi in the auricles. The mural endocardium was smooth everywhere, and there was no evidence of any rough areas in the auricular appendage.

The mitral valve showed considerable thickening, the edges appearing rolled and the cusps were slightly fused. There was a row of extremely fine warty vegetations along the line of closure.

The left ventricle was moderately thick and its endocardium presented in several places small hard calcified areas varying in size from 1 to 3 mm. cross section.

The aortic cusps were markedly thickened by very large, irregular, partly calcified vegetations which projected from both surfaces of the cusps. There was marked fusion of the commissure of the posterior and anterior cusps which were particularly thick and rolled at the edges.

The left coronary artery formed only the anterior descending branch. The right coronary artery divided immediately into two shortly after its origin.

The right ventricle measured 5 to 7 mm. at the region of the conus.

The tricuspid valve was slightly thickened and distinctly rolled at the free edge. The chordae tendineae were slightly shortened and thickened.

There were no signs of any thrombi throughout the entire length of the aorta or its main large branches. The femoral arteries were patent throughout.

**CASE 3.**—C. B., a male, aged 62 years, was admitted to the Morrisania Hospital on Dec. 31, 1930, and died on Jan. 5, 1931.

*Previous Illness.*—The patient had been well and working as a butcher until two months before when he began to notice progressive swelling of the lower extremities and shortness of breath on exertion. The swelling of the lower extremities subsided at night or when he was at rest. During the past month he had noticed ulcerations of both legs near the ankles, and these had increased in size and had not yielded to treatment although the patient had been in bed for the past month. Attacks of paroxysmal shortness of breath had set in during the past few weeks, and these had increased in frequency and had not been relieved with rest in bed.

*Physical examination* on admission to the Morrisania Hospital revealed an old man extremely short of breath with marked edema of the lower extremities. The skin over both legs was smooth, stretched and cracked in several places where edema fluid was escaping. The left leg presented on its outer aspect a little above the ankle a large ulcer about 4 cm. in diameter. It was covered by a black scab at its inferior margin. The right leg presented an ulcer about 2.5 cm. in diameter which extended only through the superficial layers of the skin.

His lips and ears were markedly cyanotic. There was active arterial pulsation on both sides of the neck. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of fair quality, the first sound being replaced almost entirely by a loud blowing systolic murmur. The heart rhythm was totally irregular with an average ventricular rate of 145 beats per minute and a pulse deficit of 45 beats. The pulses were unequal and irregular.

The blood pressure was approximately 140 mm. of mercury systolic and 80 mm. diastolic and it was practically the same on both sides.

The abdomen was soft and the liver edge was palpable 6 cm. below the costal margin in the midclavicular line. There were no signs of shifting dullness in the flanks.

*Course in Hospital.*—On Jan. 2, 1931, the patient complained of severe and excruciating pain in the whole of the right lower limb from the thigh downward. He was irrational and at times uncontrollable. The pain disappeared on the evening of that day.

On the following morning both his legs assumed a deep bluish discoloration extending from the ankle upwards almost as far as the region of the lower pole of the patella. The femoral pulses, however, were both palpable but weak. His ventricular rate was 164 beats per minute and there was a pulse deficit of over 50 beats despite the fact that he had received large doses of digitalis in the previous two days.

At 8 A.M. of Jan. 5, 1931, the patient was unusually dyspneic and disoriented. He could hardly talk. His right hand was cyanotic and presented a uniform violaceous discoloration extending as far as the middle of the forearm. The radial pulse on this side was palpable, and at first it was thought that this discoloration might have been due to pressure since the patient favored the right side.

At 2 P.M. of this day, his respirations had increased and became labored. The patient was in a stuporous condition and could hardly be aroused. The cyanosis of his right arm noted in the morning had become deeper and now extended almost to the lower part of the forearm. The fingers were almost black. It was also observed that the left hand had now become very dark in color. Both of his hands were very cold and clammy. The pulses were still present, however, but barely palpable. There was absolutely no change in the intensity of his heart sounds. Unfortunately an oscillogram was not available at this time.

The legs had now assumed a uniform black discoloration as far up as the knees. The patient died in coma at 7 P.M. of this day.

*Autopsy Findings.*—(Only points of interest are reported here.) The heart was markedly enlarged and it weighed 870 grams. The parietal pericardium was thickened and adherent to the visceral pericardium at the apex and at the base of the heart.

The left auricle was markedly enlarged. The left auricular appendage was firm and prominent. On opening the left auricle, a cylindrical thrombus 2.5 cm. in diameter was seen to extend from the tip of the auricular appendage as far as the orifice of the mitral valve. It measured 9.5 cm. from tip to tip. Its lower pole was conical in shape and fitted directly over the mitral orifice. In this region the thrombus was of a different color than the rest, and it was faceted with the imprint of the mitral valves on it. The thrombus could be easily displaced from over the orifice since it was attached only to the auricular appendage.

The mitral orifice admitted the tips of two fingers. The leaflets were smooth at their edges and no vegetations were present.

The right ventricle was hypertrophied and measured 8 mm. near the conus.

The left ventricle was concentrically hypertrophied and its wall measured 15 mm. in thickness near the apex.

The aortic orifice measured 6.5 cm. in circumference. The aortic leaflets showed many calcified nodules and the commissures of the valves were thickened.

The coronary arteries were slightly tortuous and thickened but patent throughout.

The aorta and its tributaries showed no abnormalities, and there were no thrombi or emboli in the large vessels of the extremities.

The vena cava and its branches contained no thrombi.

#### DISCUSSION

The peripheral circulatory disturbances following obstruction to the mitral orifice by an occluding thrombus of the left auricle may be of two types, either transitory or permanent. The transitory signs con-

sisting of temporary interference with the circulation to the extremities and cerebrum as observed particularly in our second case, are easily explained. When the lower pole of the loose left auricular thrombus became impacted into the mitral orifice, the diminished blood flow from the left ventricle caused by its obstruction as well as the rapid ventricular rate, resulted in absent pulsations of the peripheral vessels and the cadaveric appearance of the extremities supplied by them. It was at such times that the patient's sensorium was disoriented and mild convulsive seizures were noted. The first heart sound practically disappeared when this occurred.

It is difficult, however, to explain why sometimes only one of the lower limbs lost its circulation temporarily while at other times no pulsations or oscillometric readings were obtainable in any of the limbs. The total absence of gangrene in this patient was probably due to the fact that occlusion of the mitral orifice by the loose ball thrombus was not complete and was present for short periods at a time only, thus permitting the reestablishment of the peripheral circulation with adequate nutrition to the extremities.

Of particular interest in this case is the mode of death which was gradual and not sudden as is suspected in the presence of a loose thrombus of the left auricle. She died after she had been in coma for some time.

The more permanent circulatory disturbances observed in the other two patients came on rapidly. Their appearance undoubtedly coincided with a sufficient growth of the lower poles of the pedunculated auricular thrombi to encroach upon the mitral orifice. In this manner the nutrition of the tissues farthest away from the heart was gradually diminished and resulted in gangrene of the terminal phalanges of the fingers and toes in one case, and gangrene of the hands and feet in the other.

In the patient with hypertension (Case 3) this was probably more rapid than in the case with mitral stenosis (Case 1).

It should be mentioned here that another factor responsible for the appearance of gangrene in such patients may be the development of marantic thrombi in the larger vessels of the lower extremities as a result of the poor peripheral circulation caused by the interference with the blood flow to the left ventricle and consequently to the limbs. Such a condition is a rare association with congestive heart failure, but it was found in Battistini's first patient.<sup>3</sup> Obviously embolic phenomena to the extremities must be ruled out, but these are usually single and affect only one limb at a time.

Ulcerations of the legs, seen in our third case, were also noted by Bozzolo,<sup>2</sup> but in both instances it was probably part of the gangrenous destruction of the tissues due to the very poor circulation. We have never seen gangrene or ulcerations of the leg develop solely because



of edema of tissues. In our case the main large vessels of the legs supplying these regions presented no emboli or thrombi at autopsy.

The postulate that the underlying pathological lesion must necessarily be a mitral stenosis<sup>1</sup> in order that gangrene develop in the course of an occluding auricular thrombus is not tenable since one of our patients in whom these signs were present had hypertension during life and post-mortem examination did not reveal any stenosis of the mitral orifice.

There is one phenomenon which all of these cases including those reported in the literature present and that is a rapid and irregular heart action with a marked pulse deficit due in every instance to auricular fibrillation. This undoubtedly predisposes and favors the formation of auricular thrombi since such thrombi are not found so commonly in patients with normal sinus rhythm. The factors, however, responsible for the formation of either ball or pedunculated thrombi are still unknown.

In none of our three cases was it possible even with use of very large doses of digitalis to slow the ventricular rate materially.

The prognostic significance of occluding auricular thrombi is of great importance. The presence of severe peripheral disturbances associated with such thrombi usually presages death within a very short time after the onset of their appearance. None of these patients has been known to live longer than a little more than a month at the most.

#### SUMMARY

1. Three patients are reported in whom a clinical diagnosis of an occluding thrombus of the left auricle suspected during life was confirmed by post-mortem examination. Two of these patients had mitral stenosis and one had hypertension.

2. In one patient the diagnosis of a ball valve thrombus was suspected on the basis of the sudden and transitory appearance of peripheral vascular disturbances such as uniform discoloration with cadaveric appearance of the extremities at a time when pulsations of the vessels to these limbs were totally absent. During such periods the sensorium was disoriented, the patient was in mild shock, the skin was cold, moist and clammy, and the first heart sound was inaudible, while oscillometric readings of the limbs affected revealed no movements.

3. A diagnosis of an occluding auricular thrombus was based in one case on the rapid development of uniform discoloration with gangrene of the terminal phalanges of the ten toes and ten fingers which persisted for more than a month until death. In the other case this diagnosis was based on the rapid progressive appearance of pain and gangrene of the legs and arms with weak pulsations in the vessels supplying these limbs.

4. All three patients showed auricular fibrillation with a rapid ventricular rate and were refractory to large doses of digitalis. It is probable that the irregular heart action favored the rapid development and increase in size of the auricular thrombi. The circumstances responsible for the formation of ball or pedunculated thrombi are still unknown.

5. The mechanics of gangrene formation in the presence of an occluding thrombus of the left auricle is based upon its obstruction of the mitral orifice causing a diminished blood flow to the periphery. This is enhanced by the further incomplete diastolic filling of the left ventricle because of the rapid and irregular heart action.

6. The onset of such peripheral disturbances in patients with heart disease is of grave prognostic significance for death takes place shortly after their appearance.

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# A CASE OF ACUTE CORONARY OCCLUSION WITH ROENTGENOGRAPHIC EVIDENCE OF THE EARLY DEVELOPMENT OF AN ANEURYSM OF THE LEFT VENTRICLE\*

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THIS case of coronary occlusion is presented because of the paucity of symptoms as compared with the extent of the pathological changes present; the evidence of the presence of an aneurysm of the ventricle, coming on seemingly during the acute myomalacic stage; and the occurrence of the lesion in a relatively young individual.

## CASE REPORT

M. S. Male; aged 35 years; was admitted to the general medical service of Dr. J. Rosenthal, on November 20, 1930, complaining of pain in the left chest anteriorly and a slight hacking cough for four days previously. He had enjoyed perfect health until two weeks prior to admission. At that time he had an attack of sticking, burning pain in the epigastrium which occurred about half an hour after a meal and which lasted only a few minutes. He complained of sour eructations and belching; no tarry stools, vomiting or jaundice were noticed. Following this the patient felt well and worked for nine days. Five days before admission, while in the subway, he was suddenly seized with an attack of nausea and vomiting and a sternal burning and pressure, which was not severe, but which was accompanied by a fear of impending death. He could not go on, an ambulance surgeon was called, and he was removed to the County Hospital. The vomiting disappeared immediately, and the nausea persisted for a whole day; the sternal pain, which was not severe, was relieved in a few hours by a hypodermic of morphine. The following day the symptoms almost all subsided and within forty-eight hours the patient left the hospital against advice. Because of a slight hacking cough and slight pain in the left chest anteriorly, the patient thought "he had caught a cold" in the hospital and sought the advice of a physician. Hospitalization was advised because the patient was running a temperature of 101° to 102° F.

*Family History.*—Negative. Married eight years; wife had two children, both living and well.

*Past History.*—The patient was a truckman and worked hard. He smoked about three cigars and drank about three cups of coffee each day. He recalled no serious illnesses nor any surgical procedures. No cardiac pain, palpitation, dyspnea on exertion or edema prior to the onset of the present illness.

*Physical Examination* at the time of admission revealed a muscular young adult male in good nutrition, of the sthenic type. He did not appear very ill. No dyspnea or cyanosis was noted. Pressure over the styloid processes elicited no response, indicating marked hyposensitivity. Libman<sup>1</sup> has emphasized the importance of estimating a patient's reaction to pain in the interpretation of his symptoms. This case illustrates the point well. The head showed no gross abnormalities. Eyes and ears were negative. The pupils were regular, equal and

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reacted both to light and in accommodation. The eye grounds were normal and showed no evidence of vascular sclerosis. Nose negative. The tongue had a thin whitish coat. Fauces and pharynx negative. Neck negative. The chest was slightly pigeon breasted. The lung fields were clear throughout. The heart impulse was visible and palpable somewhat to the left of the midclavicular line in the fifth space. The signs were more marked in this localized area both on auscultation and on palpation over the rest of the precordium. The borders percussed as follows: *left*—3 cm. from midsternal line in the second space, 8.5 cm. in the third, 11 cm. in the fourth and 12 cm. in the fifth; *right*—2.25 cm. from midsternal line in the second space and 3 cm. in the third and fourth. The heart action was regular, with a rate of 70. Heart sounds were somewhat distant and not of good quality; the first sound at the apex was barely audible; A-2 was greater than P-2; no murmurs were heard. The abdomen and extremities appeared normal. No edema was present. None of the stigmata of syphilis could be found. Right carotid sinus pressure caused a cardiac standstill for a short period.



Fig. 1.—X-ray picture taken on the sixth day of illness, showing aneurysm of the left ventricle.

*Laboratory Data.*—The temperature ranged up to 101.4° F. the first six days of his hospital stay; from then on it was normal. The pulse rate ranged from 88 to 68. Blood pressure on admission was 110/70 mm.; on the eleventh day of his illness it was 90/60; thereafter, it gradually rose until on the day of discharge from the hospital his blood pressure was 125/80; two months later it was 170/110. On the eighth day of his illness his blood count was 17,800 white cells and 82 per cent polys.; on the twelfth day of his illness, or the eighth day of his stay in the hospital, his blood count was 8,200 white cells and 64 per cent polys.; from that time on the blood counts were normal. Sedimentation time was fifteen minutes eight days following the occlusion, and persisted low up to the eighteenth day of his illness when it was found to be sixty minutes; from then on it gradually increased. Red blood cell count was 5,120,000 and hemoglobin was 90 per cent. Blood Wassermann, Kahn, sputum, urine and blood chemistry determinations were all negative.

Roentgenological studies of the chest were made on the second day in the hospital and were reported as follows by Dr. M. G. Wasch: "The heart is considerably enlarged, especially to the left, where the apex assumes a rather globular contour and bulges in an unusual manner. Pulsation therein is synchronous with the cardiac borders so that the condition must be considered intrinsic. The configuration strongly suggests an aneurysm of the left ventricle." Frequent restudies were made over a period of three months and showed practically no change. The cardiac silhouette is presented in Fig. 1.

In Fig. 2 are given electrocardiographic tracings taken on the patient's third day in the hospital. They show a regular sinus rhythm with a rate of about 70. The P-wave is inverted in Lead III. The P-R interval is within normal limits. The main deflections in all leads are definitely notched. The deep S-1 and high R-3 indicate a right axis deviation. The S-T interval is elevated above the

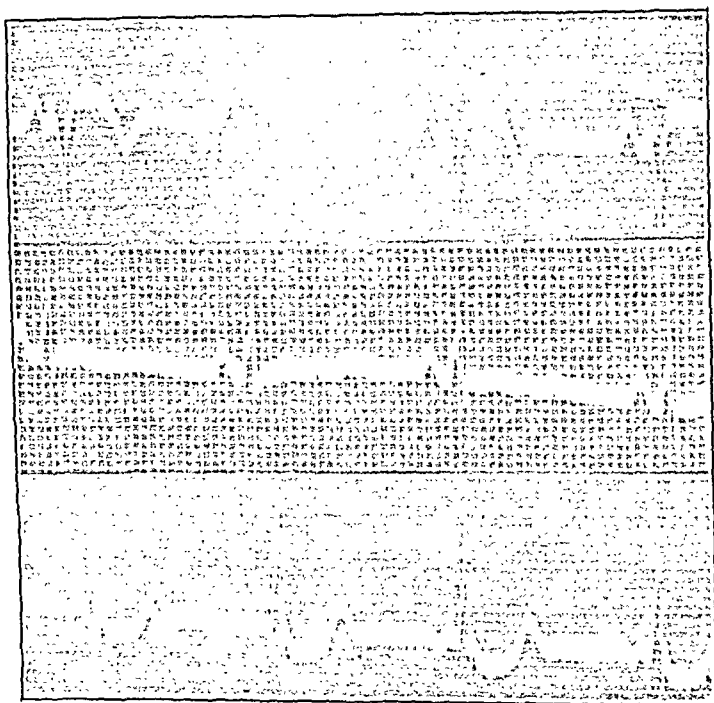


Fig. 2.—Electrocardiogram taken seven days following the coronary occlusion.

iso-electric line in Lead I and depressed below it in Lead III. The T-wave is large, coved and sharply inverted in Lead I and it is isoelectric in Lead II.

Electrocardiographic studies were made every other day up to the time of the patient's discharge from the hospital on December 16, 1930. The tracing taken on the day of discharge is presented in Fig. 3. Compared with Fig. 2 it shows a return of the S-T interval toward the base line and elongation with sharper coving of the T-1 which has become higher than the R-wave. T-2 is upright; T-3 is sharply pointed and higher than the R-3.

The few symptoms that the patient presented on admission cleared within the first seventy-two hours in the hospital. He showed no signs of cardiac embarrassment at any time. Activity was forbidden, but at the time of his admission to the hospital he experienced no difficulty whatsoever in standing or walking. His clinical course in the hospital was uneventful, and when last seen, three months following the onset of symptoms, the patient was enjoying moderate activity without pain or dyspnea. An electrocardiogram (Fig. 4) taken on February 21, 1931,

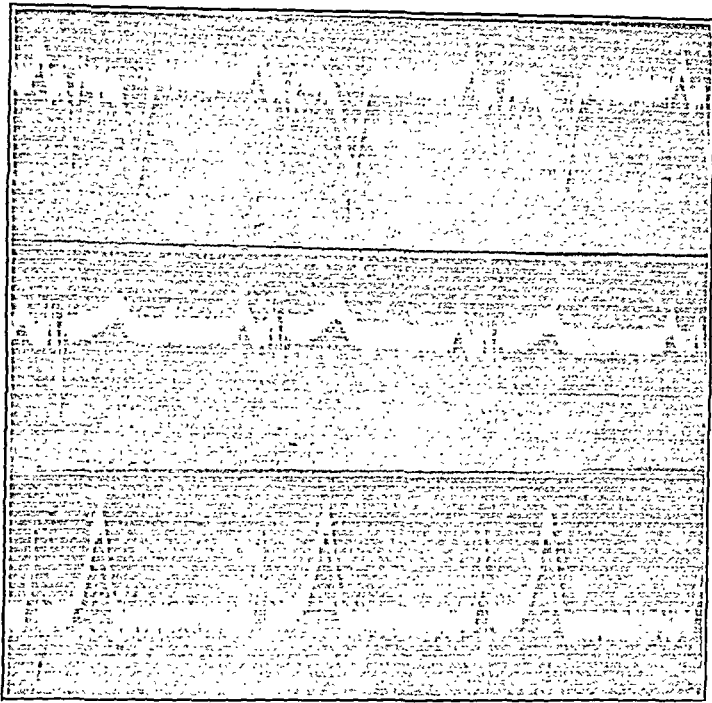


Fig. 3.—Electrocardiogram taken immediately before discharge from the hospital. Note the voltage of the T-waves in the first and third leads.

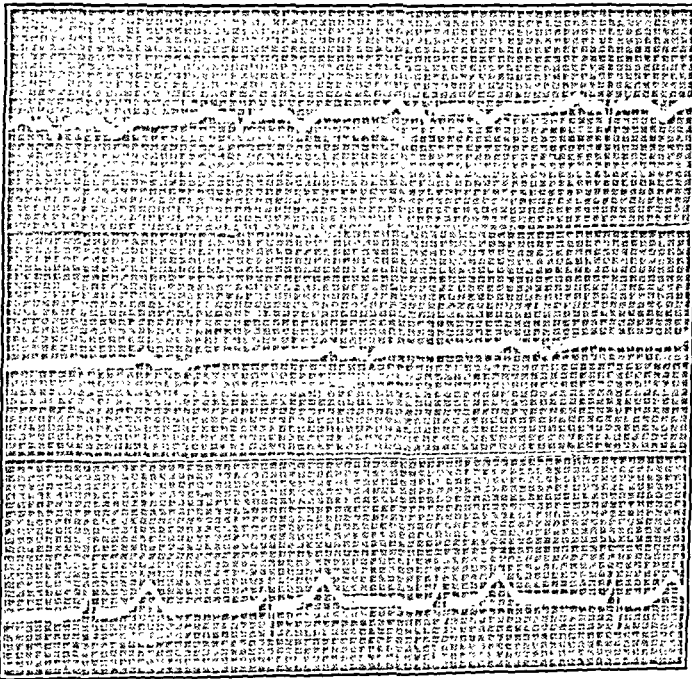


Fig. 4.—Electrocardiogram taken on February 21, 1931, at the Out-Patient Department. Note the extreme low voltage of the main deflections compared with the electrocardiograms taken while patient was in the hospital.

in the Cardiac Clinic, shows a regular sinus rhythm, ventricular rate 78. All main deflections are of very low voltage and slurred. T-1 is inverted; T-2 is iso-electric. These findings are indicative of rather severe myocardial disease.

#### COMMENT

The diagnosis of acute coronary occlusion and aneurysm of the left ventricle is, it appears to us, warranted by the evidence described above. Whether or not his recent illness represented the patient's first major cardiac insult may be questionable. To go with the marked x-ray and electrocardiographic changes presented, one would expect an extensive cardiac history. The patient was questioned very carefully in regard to the presence of cardiac pain, palpitation, dyspnea on exertion or edema prior to the onset of this illness, and he specifically denied having had any of these complaints at any time previously.

An aneurysm of the ventricle usually results from a dilatation of a healed fibrous area following a myomalacia cordis, and a definite period of time usually elapses between the original insult and the aneurysm. More often it is the result of several attacks. In this case, however, it would appear, from the history and the findings, that the aneurysm of the ventricle followed very shortly after this patient's cardiac insult. The complete absence of a history of previous attacks, as shown by the absence of pain, symptoms of cardiac insufficiency, and any of the pain equivalents of a coronary occlusion often found in hyposensitive individuals,<sup>1</sup> makes us feel that this lesion is the direct result of the recent coronary occlusion and is an aneurysmal dilatation of a fresh myomalacia.

In this diagnosis we have relied to a considerable extent upon the x-ray and electrocardiographic findings. The diagnosis of aneurysm of the heart is seldom made with certainty during life, but in this instance it appears to lack only post-mortem confirmation. B. S. Oppenheimer and H. Mann<sup>2</sup> state that the most common site for cardiac aneurysm is the apex of the heart and the middle or lower third of the anterior wall of the left ventricle, involving also the neighboring ventricular septum; with the next most common site as the posterior wall near the auriculoventricular ring. The aneurysm in this case is probably in the favorite site.

Another interesting feature of this case is the relative youth of the patient. Coronary thrombosis is rightly regarded as a disease of advanced years. One should bear in mind, however, the fact that it is not infrequently found in an individual under forty. Levine<sup>3</sup> gives the average age of 145 cases as 57.8 years, and presents in his series three cases (2 per cent) under forty years—two at thirty-nine years and one at thirty-six years. The patient observed by us was thirty-five years old. Lues was carefully excluded in this patient.

## SUMMARY

An aneurysm of the left ventricle, the clinical and roentgenological symptoms of which were noticed in the first few days following a coronary occlusion in a comparatively young man, is reported.

We wish to thank Dr. Joseph Rosenthal for his permission to report this case.

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# Department of Clinical Reports

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## THE ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING LIGATION OF DESCENDING BRANCH OF THE LEFT CORONARY ARTERY IN MAN

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CONCLUSIONS as to the electrocardiographic findings in coronary artery disease have been arrived at by two methods: first by a study of electrocardiograms from individuals presenting symptoms of coronary disease and from those proved at autopsy to have coronary disease. This is what we might call a clinico-pathological study. A second method of approach has been study on experimental animals. The nature of the problem has made experimental study on man impossible. This paper is a report of findings under experimental conditions made necessary by an emergency. It presents a series of electrocardiograms obtained after ligation of the descending branch of the left coronary artery.

### CASE REPORT\*

J. H., a colored male aged 18 years, was admitted to the Emory University division of Grady Hospital on January 8, 1931. His chief complaint was stab wound of the left chest. At 10 P.M. on the date of admission he was stabbed in the left upper chest with a knife. He ran 30 or 40 yards and fell to the ground. He was picked up and brought to the hospital at once. At that time he was conscious but extremely restless. His clothing was covered with blood. Both pupils were dilated. His extremities were cold and clammy and radial pulse was imperceptible. His heart rate which at first was 90 per minute soon dropped to 60. He was thought to be in a state of cardiac tamponade and was sent at once to the operating room. Operation, by D. C. Elkin, was begun at 10:50 P.M. The heart was exposed and a penetrating wound of the pericardium found. With each cardiac systole blood spurted from this wound. The wound in the pericardium was enlarged and the pericardial cavity found to contain about 250 c.c. of clotted blood. There was a stab wound which penetrated the right ventricle near the interventricular septum. It ran parallel and very close to the descending branch of the left coronary artery in its middle third. In the course of the operation this artery was found to have been cut. Whether this injury had occurred at the time of the stab wound or accidentally during the operation could not be stated. The artery was tied by a double ligature. Operation was completed at 11:40 P.M.

\*A detailed report of this case from the surgical standpoint is being prepared by Dr. D. C. Elkin for publication elsewhere.

*Postoperative Course.*—On the third day there was a definite to-and-fro pericardial friction rub which persisted until the sixth day. The operative wound healed nicely and all sutures were removed on the sixth day. At no time did the heart show any abnormalities of rhythm. On the eighth day he complained of pain in the epigastrium and examination showed a pleural friction rub in the lower left axilla and a few moist râles at the left base. These findings gradually decreased; his temperature reached normal, and on the twentieth day he was out of bed. He was dismissed from the hospital on February 6, 1931, and at present (March 26, 1931) is symptom free and apparently completely recovered.

Electrocardiograms were taken by the three standard leads just before operation (10:50 P.M.), just after operation (11:50 P.M.), and at frequent intervals during his stay in the hospital. Later tracings were obtained with difficulty because the

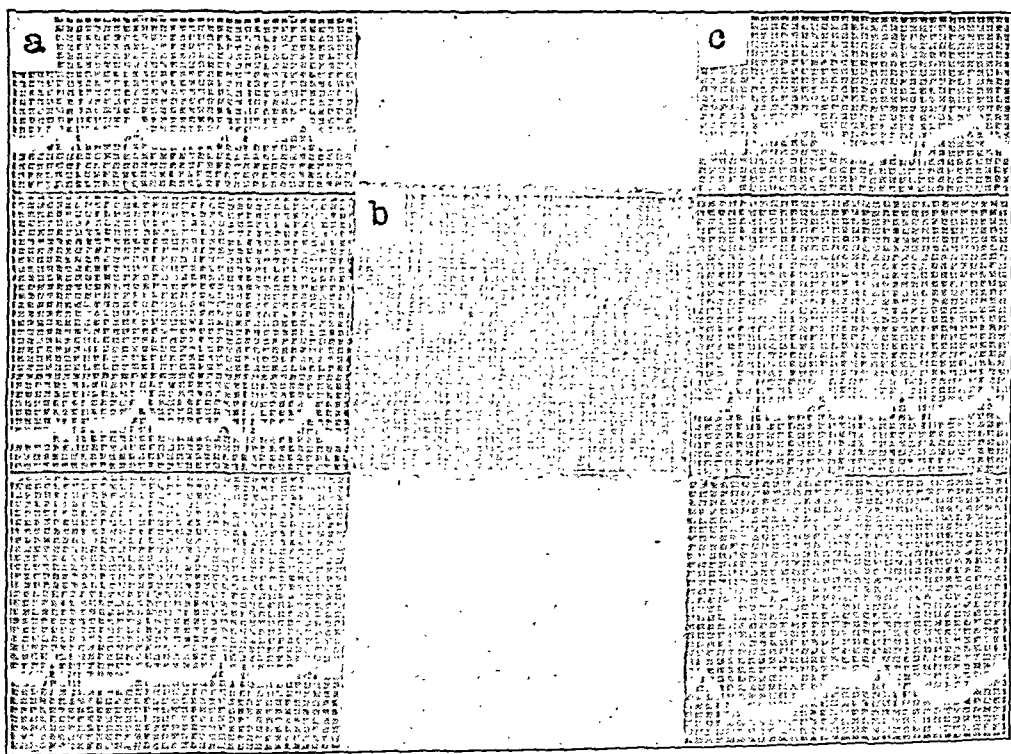


Fig. 1.—(Jan. 8) *a.* Before operation. Changing form of P in Lead II. *b.* During operation. Bizarre complexes. Ventricular premature beats. *c.* Ten minutes after operation. Elevation of R-T in Lead I and depression in Lead III.

patient had to serve a period of one month in jail. An incomplete record in Lead II was taken during operation.

Before operation, during the state of cardiac tamponade, the only outstanding abnormality was a changing form of P-wave in Lead II (Fig. 1*a*). This was probably the result of irritation of the auricles by blood within the pericardium. During operation (Fig. 1*b*) the complexes were of bizarre forms and quite irregular. The predominating type of complex was a ventricular premature contraction. These were thought to be due to mechanical stimulation produced by the operative procedure. As early as ten minutes after the operation (Fig. 1*c*) definite change was observed in the R-T interval. In Lead I there was a slight definite elevation of the take-off of T while in Lead III the R-T interval was depressed and convex downward. On the second day after operation (Fig. 2) the T-wave showed maximum change. In Lead I and II there was a very high take-off. The

first definite change in Q-3 was noted at this time. It measured 3.4 mm. which was a definite increase over previous records. In subsequent records (Figs. 3 and 4) the T-wave was observed to gradually approach the iso-electric line. It became isoelec-

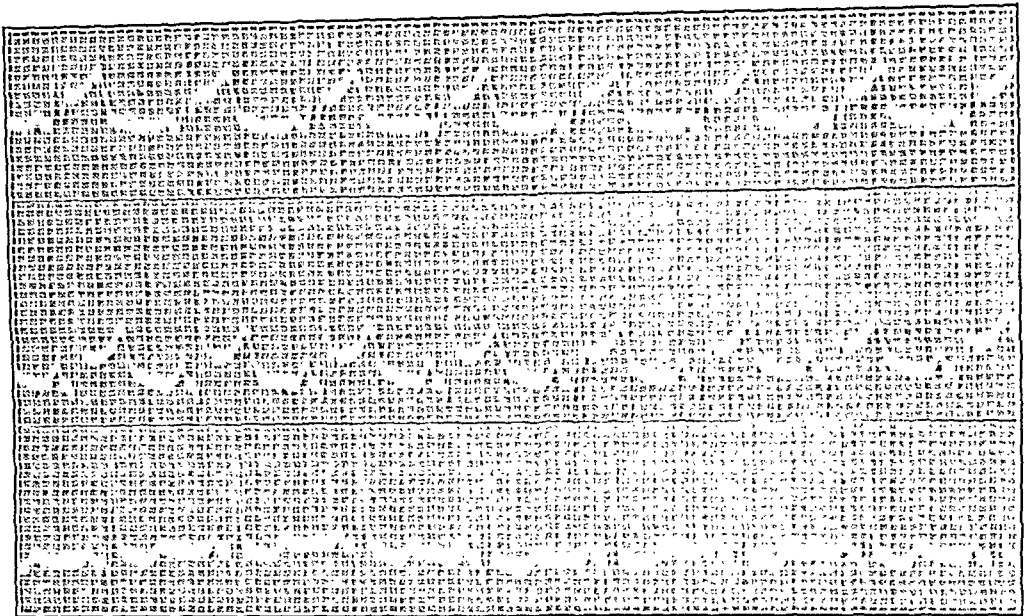


Fig. 2.—Second day (Jan. 10). Maximum change in R-T interval. Increase in Q-3.

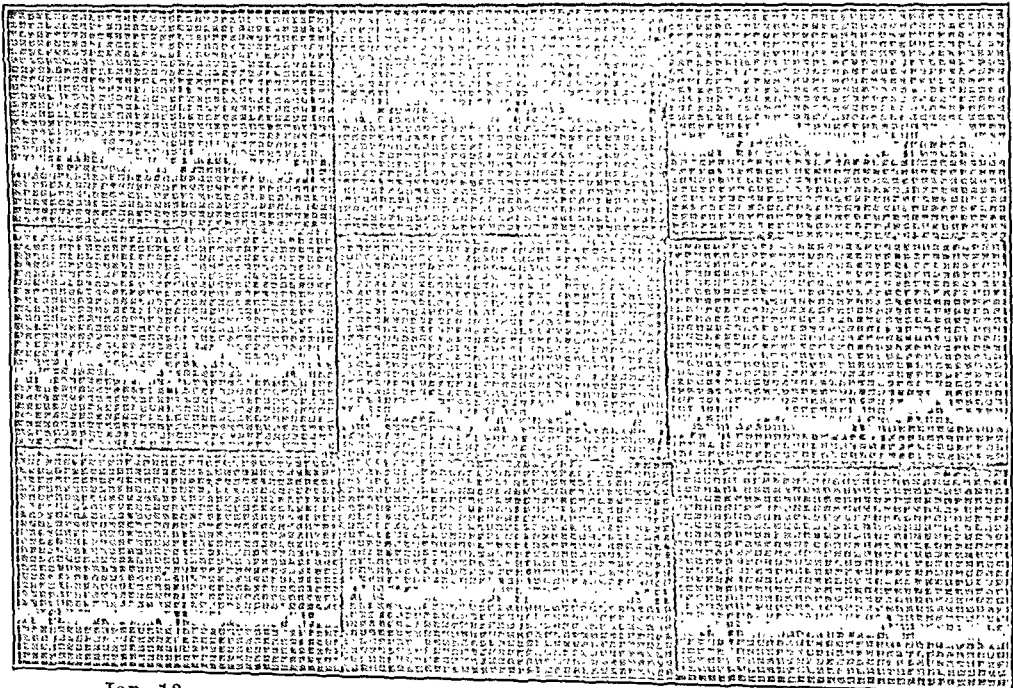
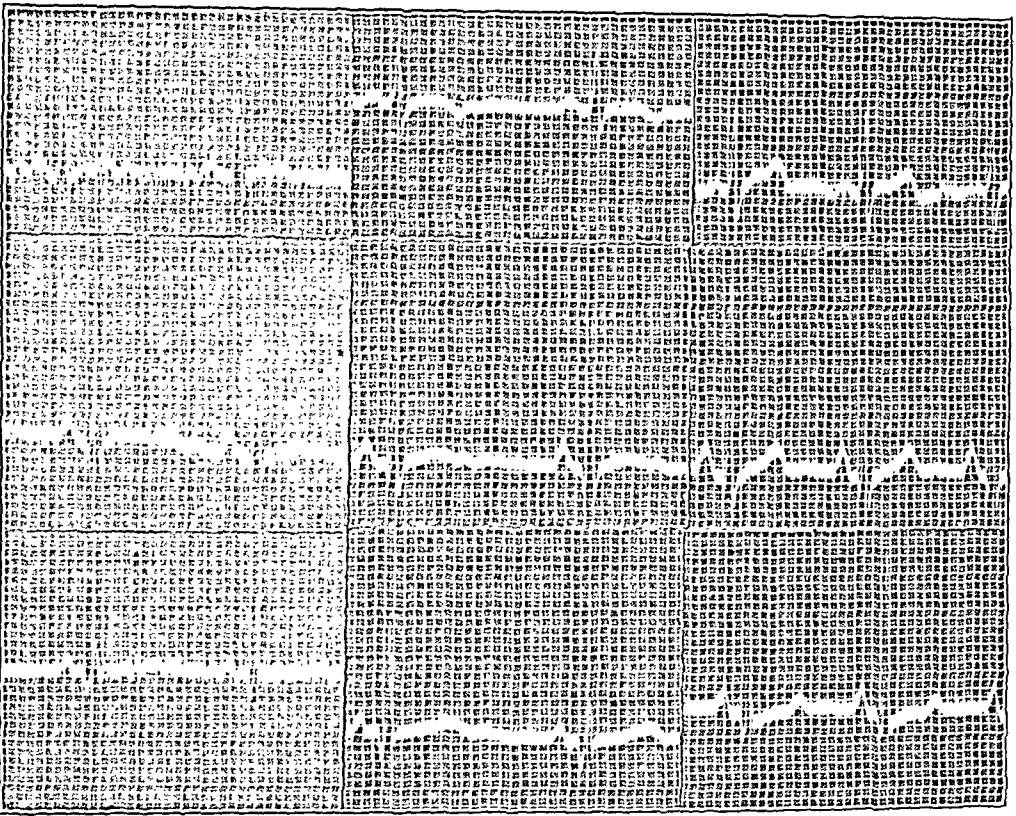


Fig. 3.—Fourth, fifth and sixth days. T gradually approaches iso-electric line. Q-3 shows maximum change on fifth day.

tric on the twelfth day and inverted sharply on the sixteenth day. On the seventy-seventh day it had become upright in all leads. The Q-wave in Lead III showed a progressive relative increase up to the fifth day. From the fourth to sixth days inclusive it was as much as 25 per cent of the greatest deflection of R (Lead II). From

that time on it gradually decreased. These changes may be followed in Fig. 5. The values represented in the curve are averages from measurements in seven complexes

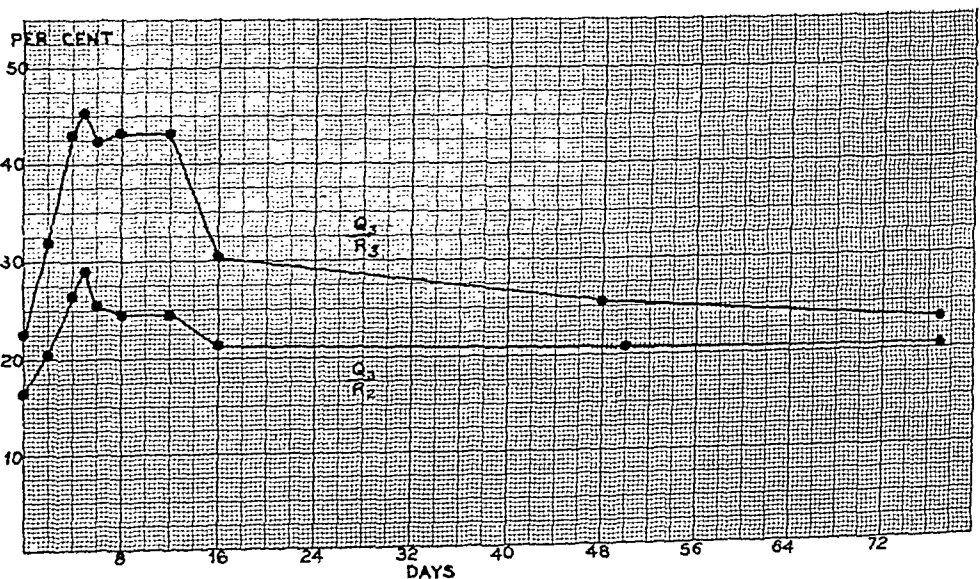


Jan. 20

Jan. 24

March 26

Fig. 4.—Twelfth, sixteenth, and seventy-seventh days. Iso-electric T changes to sharply inverted T and then becomes upright again.



of each lead. With the progressive increase in magnitude of Q-3 there was also a slurring of this same wave at its apex. With decrease in magnitude the slurring decreased.

## COMMENT

A report of one case similar to the above was made by Smith<sup>1</sup> and Davenport.<sup>2</sup> Their first electrocardiogram was obtained on the nineteenth day after operation. At that time there was inversion of T in all leads. The T-wave was found upright after eight and one-half months.

Pardee<sup>3</sup> has recently called attention to a relative increase in size of the Q-wave in Lead III in records with a left axis deviation or a normal axis. He found that the majority of such records were obtained in patients with the anginal syndrome. Along with the increase in Q-3 in such patients he often found inverted T in Lead III or in Leads II and III. Where Q-3 is greater than 25 per cent of the greatest R or S it is considered abnormal. Wilson<sup>4</sup> has referred to a large Q in Lead III occurring in coronary occlusion.

The curve shown in Fig. 5 is not presented with the idea in mind that its form, duration or magnitude of changes represents what might occur in a similar case or in a patient with coronary occlusion, but it does definitely illustrate that the Q-wave in Lead III has undergone considerable change. The changes in the R-T segment do not differ from those often described before. Decrease in amplitude of QRS was not a remarkable feature of this case. Abnormalities of rhythm were not observed.

## SUMMARY

After the unavoidable ligation of the descending branch of the left coronary artery in man the following changes were observed in the electrocardiogram:

1. Changes in the T-wave. (a) Definite elevation of take-off in Lead I and depression of the R-T interval in Lead III within ten minutes after operation (probably thirty minutes after ligation). (b) Maximum change within forty-eight hours. (c) In Leads I and II it gradually descended on R and became isoelectric in twelve days, inverted in sixteen days, and upright in seventy-seven days.

2. Changes in the Q-wave in Lead III. (a) Increase in size. It exceeded 25 per cent of the greatest R from the fourth to sixth days. Maximum increase was present on the fifth day. (b) Slight slurring at its apex.

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PERSISTENT TRUNCUS ARTERIOSUS: CARDIAC  
HYPERTROPHY, DYSPHAGIA, DEATH ON  
ELEVENTH DAY

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CONGENITAL cardiac defects similar to the one here recorded have been previously described several times, yet the condition is of sufficient rarity to justify placing on record another instance. Dr. Maude E. Abbott<sup>1</sup> in 1927 had collected but 23 cases. Most persons with persistent truncus arteriosus usually die shortly after birth. The defect, however, is not always incompatible with the attainment of adult life and activity as instanced by the last two cases which we have seen reported. In one<sup>2</sup> the patient was twenty-five years of age when killed in an automobile accident, and the malformation was discovered only at necropsy. In the other<sup>3</sup> the patient died of a superimposed endocarditis at twenty-two years of age. The present instance is unusual in that dysphagia was the main symptom calling attention to serious disease. Roentgen-ray pictures were obtained, and from them some gross malformation of the heart was diagnosed during the brief life of the patient, although the exact nature of the lesion was not revealed until necropsy.

CASE REPORT

*Clinical Findings.*—P. J. E., white female. Delivery normal, weight 7 lb. No abnormalities noted at birth except a thick mat of black hair on head and small, poorly developed ears. Older children in family normal, living and well.

Cry at all times rather weak. Slight cyanosis present at all times with severe exacerbations of marked cyanosis several times a day. Never able to nurse well. Chief symptom, however, was an apparent difficulty in swallowing. The breast was taken rather eagerly at first but was soon released and was followed by an almost immediate regurgitation of milk through the nose and mouth, so that the child received but little nourishment during its eleven days of life. Between feedings there was an almost constant drooling of saliva, which at times accumulated in the throat to such a degree that a suction apparatus had to be used to prevent asphyxia. The symptoms were so suggestive of an obstruction of the esophagus that a catheter was passed, barium sulphate given and roentgen-ray pictures were made. (See Figs. 1 and 2. *E* points to barium shadow in esophagus, *S* to stomach.)

At eleven days of age the cyanotic periods increased in frequency and severity, and the baby grew weaker and died.

*Roentgen-Ray Examination.*—Antero-posterior view shows an enormously hypertrophied right ventricle and right auricle. The right auricle expands upward and to the left. The angle which normally exists between the ascending aorta and the right auricle is not seen as the auricle extends well to the right and upward. There is an immense expansion of the heart in the horizontal diameter. There are no recognizable subdivisions of the heart into its different parts. Lateral view shows the right ventricle enormously enlarged upward and forward, filling in the retro-

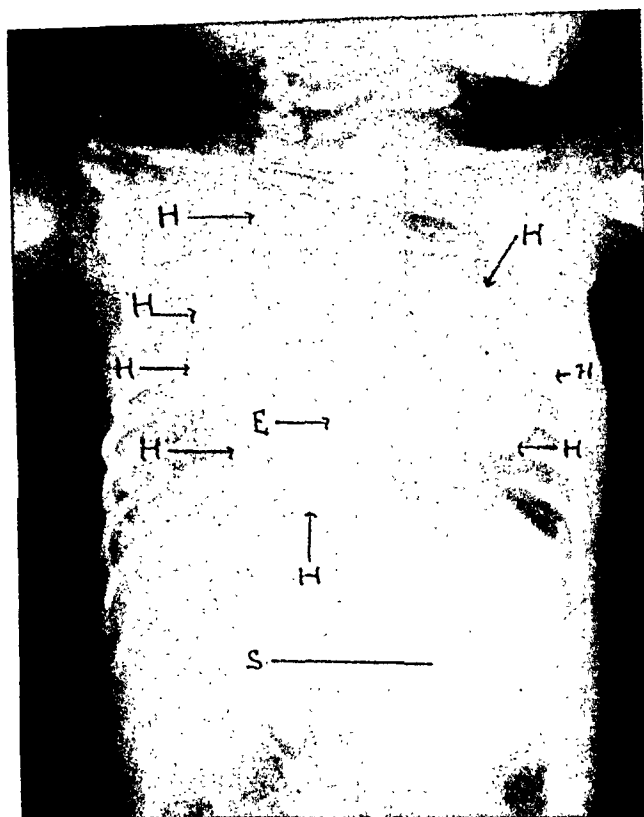


Fig. 1.—Antero-posterior roentgenogram of chest. Enlarged heart shadow, *H*; esophagus with small quantity of barium sulphate, *E*; stomach outlined by barium, *S*.

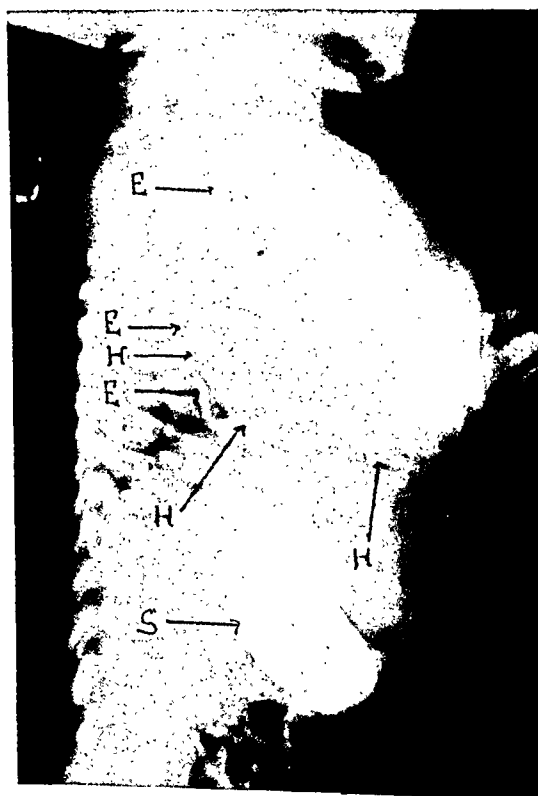


Fig. 2.—Lateral roentgenogram of chest. Enlarged heart shadow, *H*; esophagus, *E*; and stomach, *S*.

sternal space, which normally exists between the sternum and right ventricle. The retrocardiac space is almost filled by the large right auricle, and the esophagus (outlined by barium) is seen pressed upon (*H*, Figs. 1 and 2).

*Post-Mortem Examination.*—Body is that of a white female infant in the first few days of life. The scalp is covered with a thick suit of nearly black hair. The ears are small and placed rather obliquely on the head, the upper border of the pinna being somewhat diverted backward. The thorax is somewhat enlarged. On opening the thorax the heart is found to be enormously enlarged, occupying most of the anterior portion of the thoracic cavity, the lungs being displaced laterally and backward. There is a slight excess of dark colored serous fluid in each pleural cavity and a few small hemorrhagic spots are seen on each lung. The usual lobes of the lungs are indicated by rather shallow divisions. The cardiac notch of the

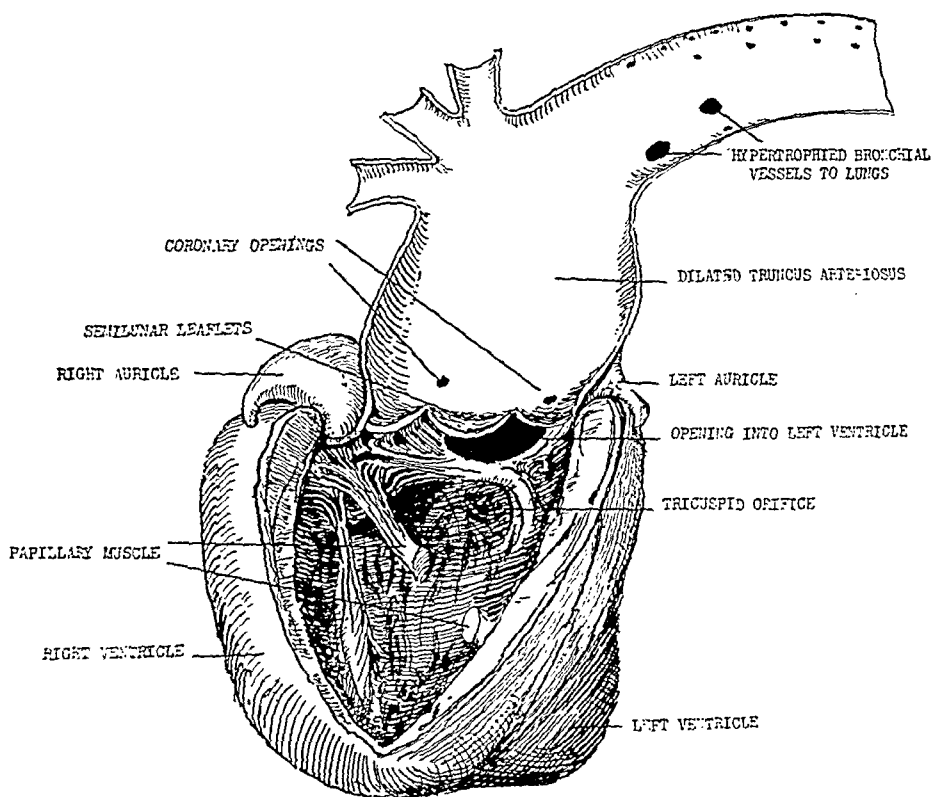


Fig. 3.—Anterior view of heart with the right ventricle opened and the truncus arteriosus opened throughout its extent.

left lung is very large, being nearly an equilateral triangle, the sides measuring about 35 mm. The middle lobe of the right lung is poorly defined and largely blended with the upper lobe. The lungs appear well aerated.

The pericardium is normal.

The thymus gland is normal in appearance and not enlarged.

The heart is greatly hypertrophied and the right side is noticeably larger than the left. The most conspicuous feature of the heart is the absence of the pulmonary artery and the origin of the truncus arteriosus from the right ventricle in the tri-hedral angle formed by the right auricle, the right ventricle and the left auricle. No vessel emanates from the left ventricle. In about the location where the aorta normally should arise from the left ventricle there is a well defined opening, admitting a lead pencil, diameter 8 mm., into the right ventricle and directly beneath the right posterior cusp of the aortic valve.



The right ventricle measures vertically 50 mm.; laterally, at the widest point, 35 mm.; wall at thickest point toward the base, 7 mm.; and at thinnest point toward the apex, 2 mm. The interior of its chamber aside from its large size appears normal. The tricuspid valve appears normal. No pulmonary artery drains it but the truncus arteriosus instead. Beneath the right posterior leaflet of the aortic valve is an 8 mm. opening into the left ventricle.

The right auricle appears essentially normal aside from its large size. It is in communication with the left auricle by a patent foramen ovale, 8 mm. in diameter.

The left ventricle is hypertrophied, but not nearly so much as the right; ventrically it measures 35 mm.; laterally, about 15 mm.; thickness of its wall in middle portion, 5 mm. No vessel leads from it, but it is in communication with the right ventricle by an 8 mm. opening occurring directly beneath the right posterior leaflet of the aortic valve at about the point where the aorta should normally arise. The mitral valve appears normal.

The left auricle is essentially normal. It has four openings for pulmonary veins into it.

The ascending portion of the truncus arteriosus resembles the normal aorta and from it arise two normal coronary arteries. The width of the truncus at its origin is about 20 mm. The first part of the arch is sacculated and its width is about 27 mm. From the summit of the arch the usual innominate and left carotid and subclavian arteries appear to arise. The descending portion of truncus arteriosus gives off ventrally two relatively large branches, hypertrophied bronchial arteries, the more superior leading to the right lung and the more inferior to the left lung. The usual small intercostal arteries are present.

The relationships of the various parts of the heart and vessels are shown in Fig. 3.

Abdominal viscera show no essential abnormalities.

The clinical symptoms are readily accounted for in view of the pathological findings. The greatly hypertrophied heart, in large part filling the thoracic cavity, pressed upon the esophagus and interfered with swallowing, nursing and nutrition. The lungs restricted in space by pressure of the much enlarged heart prevented complete aeration of the blood. Further aeration of the blood was also interfered with by the inadequacy of two hypertrophied bronchial arteries from the truncus arteriosus, acting for the lacking pulmonary artery and its branches. The hypertrophied bronchial arteries are not relatively as large as the bronchial arteries pictured in the adult case reported by Zimmerman.<sup>2</sup>

#### SUMMARY

A case of the rare anomaly, persistent truncus arteriosus, is recorded. The heart was enormously hypertrophied. Dysphagia was the main symptom calling attention to the defect. Necropsy revealed a persistent truncus arteriosus, and an opening from the left ventricle into the right ventricle. Enlarged bronchial arteries functioned as pulmonary vessels. Death occurred at eleven days of age.

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# CONGENITAL DEXTROCARDIA WITH SITUS TRANSVERSUS COMPLICATED BY HYPERTENSIVE HEART DISEASE; ELECTROCARDIOGRAPHIC CHANGES\*

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THAT congenital dextrocardia with complete situs transversus produces characteristic electrocardiographic alterations is well known. These changes consist of reversal in direction of all the waves in Lead I,<sup>2, 3, 4, 5, 6, 7, 8, 9</sup> The other leads remain unchanged. The reversal in direction of the waves results from the complete transposition of the anatomical and the electrical axis of the heart. This peculiar congenital anomaly does not interfere with normal life, and is frequently discovered accidentally in the course of a general examination. It is a curious fact that the electrocardiogram is not altered unless the malposition of the heart is accompanied by transposition of the abdominal viscera. This indicates, however, that with complete situs transversus, the axis of the heart is sufficiently altered to bring about reversal of the action currents of the heart, and the graphic inscription is reversed in Lead I, which, in general, represents the activity of the left side of the heart.

In persons who possess this anomaly, cardiac diseases of various types may develop as well as in perfectly normal persons. It is apparently unusual for superimposed cardiac disease to cause alterations in the already abnormal Lead I of the electrocardiogram. Such alterations did occur in the case reported here.

## REPORT OF CASE

A man, aged 59 years, came to The Mayo Clinic because of weakness that had persisted after the occurrence of cerebral thrombosis four years previously. The only significant fact in the family history was that the patient's father had died at the age of 78 years, from cerebral hemorrhage. The patient had had scarlet fever at the age of 6 years, typhoid fever as a young man, frequent tonsillitis about 23 years prior to examination, mild pleuritis, and malaria. He had suffered from migraine for many years. He apparently had possessed good health until 4 years before he came to the clinic, when weakness suddenly had developed in the right leg and arm, while he was driving his car. There had been no loss of consciousness and no difficulty in speech, and he had been able to drive the car home. The function of the right leg and arm had improved rapidly but never had returned to normal. A physician had made a diagnosis of high blood pressure. Thereafter there had been persistent weakness, difficulty in mental concentration at times, peculiar behavior at intervals, and rather thick speech occasionally. Moderate exertion had caused the patient to become somewhat breathless, but there had been no evidence of congestive heart failure. There were no further complaints of significance.

\*From the Section on Cardiology, The Mayo Clinic.

The patient was slightly overweight. He appeared older than his age. The teeth showed evidence of much dental work and the mouth was reddened. The peripheral arteries were moderately thickened. Cardiac dullness was found to extend to the right, and the apex beat was visible just beyond the right nipple. The total area of cardiac dullness was definitely increased beyond normal. There was a rough, blowing, systolic, basal murmur. The systolic blood pressure ranged from 230 to 262 mm. of mercury, and the diastolic pressure from 140 to 142 mm. There was moderate (graded 2) sclerosis of the retinal arteries, with moderate retinitis of the type of severe benign hypertension. There was also thrombosis of a small inferior vein of the right retina, with hemorrhage. A detailed neurological examination disclosed arteriosclerosis of the vessels of the central nervous system and residual evidence of previous cerebral vascular interference. The blood count was normal, and there was only a faint trace of albumin in the urine. The Wassermann



Fig. 1.—Position of the heart, in a case of situs transversus.

test of the blood was negative. There were 32 mg. of urine in each 100 c.c. of blood. Roentgenographic examination of the thorax verified the presence of dextrocardia (Fig. 1); the heart was enlarged and the aorta was tortuous and slightly dilated. Fluoroscopy of the gastrointestinal tract revealed that the organs were transposed. Electrocardiography revealed sinus rhythm and reversal of the R- and P-waves in Lead I. The T-wave was upright.

The diagnosis was congenital dextrocardia with complete situs transversus, hypertensive heart disease, severe benign hypertension, artero-sclerosis of the vessels of the central nervous system and the peripheral arteries, and residual evidence of previous cerebral thrombosis.

#### COMMENT

The interesting and unusual feature of this case was revealed by the electrocardiogram (Fig. 2). As previously stated, congenital dextrocardia with complete situs transversus is always associated with

complete reversal of all the waves in Lead I. Here, however, the T-wave in Lead I was upright. Barnes and Whitten, and I<sup>20, 21</sup> are among those who have shown the frequent occurrence of T-wave negativity in Lead I of the electrocardiogram with hypertensive heart disease. Barnes and Whitten clearly showed that the inversion of the T-wave in Lead I, or in combined Leads I and II, occurred with unusual uniformity among patients who gave evidence of strain predominantly of the left ventricle. This interpretation is exclusive of myocardial infarction, in which different and additional factors are at work. In this case, in which inversion of the T-wave in Lead I was

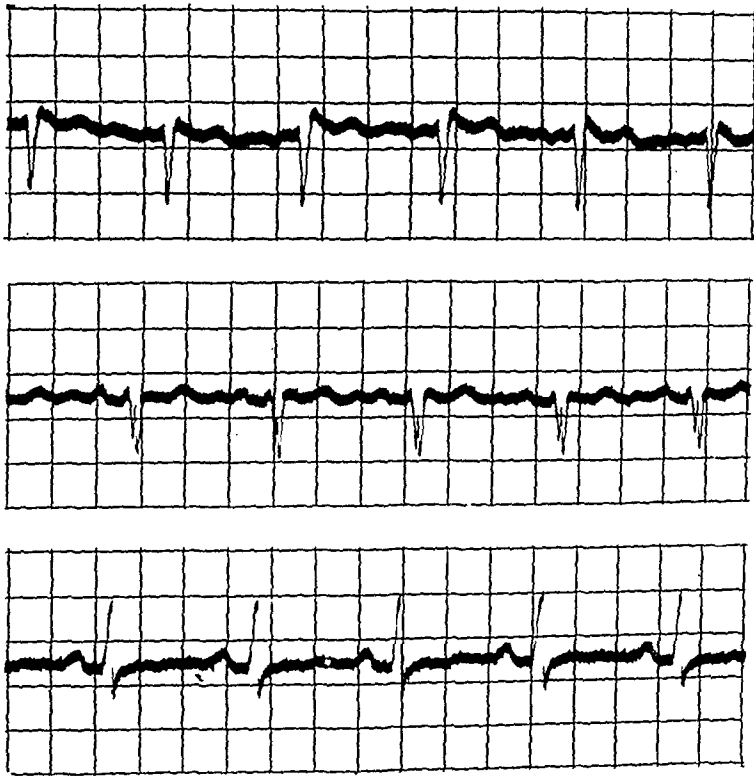


Fig. 2.—Electrocardiograms in a case of situs inversus.

anticipated as part of the disturbance attending congenital malposition of the heart, it was upright. Undoubtedly the upright position of the T-wave in this case represented the counterpart of T-wave negativity under conditions in which the heart is normally placed. It was, therefore, evidence of strain predominantly of the left ventricle, resulting from the severe hypertension.

The coexistence of congenital dextrocardia with complete situs transversus and acquired cardiac disease, in relation to additional changes in Lead I of the electrocardiogram is interesting, and study of additional cases unquestionably will reveal other unusual observations.

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# CALCIFIED PLAQUE OF THE AORTA AT THE ENTRANCE OF A PATENT DUCTUS ARTERIOSUS: A POINT IN DIAGNOSIS\*

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## CASE REPORT

E. M., a colored woman, aged 33 years, was admitted to the Jefferson Hospital, May 20, 1931. She complained of pain in the right chest and shortness of breath.

The family history was negative.

Past history.—Pelvic inflammatory disease in 1925 and again in 1930; operated upon in 1925 and 1926. The patient had five living children and two miscarriages.

The present illness began about five weeks before admission with fever and general malaise followed by slight cough, then severe chills and high fever. Pain in the right side and increasing shortness of breath occurred just before admission.

Physical examination showed a poorly nourished young colored woman with some dyspnea, no clubbing of the fingers and no evidence of petechiae. The pulse rate was 120 and regular. The pupils reacted to light and in accommodation. The heart; apex beat was forceful in the 6th interspace at the anterior axillary line; left ventricle dulness apparently extended into the mid-axilla. The first sound had poor tone and there was a slight systolic murmur at the apex, also a rough systolic murmur over the pulmonary area. No thrill was felt. The right ventricle apparently was not extended. The lungs were resonant with the exception of the right base posteriorly and lower right axilla, where there was slight impairment of the percussion note but no râles. The abdomen was held rather rigidly. No organs or masses were made out. There was no edema of the legs. The knee jerks were active. About 5 c.c. of slightly turbid fluid were withdrawn from the base of the right chest posteriorly. No more could be obtained. No organisms were obtained from the fluid. The blood count on admission was hemoglobin 52 per cent, R.B.C.—2,940,000, W.B.C.—15,200 with 81 per cent polynuclears. On May 29 the W.B.C. were 27,000, on June 2, 31,000. The blood Wassermann was 4 plus. The blood culture was negative. The sputum was negative for tubercle bacilli. The urine contained a trace of albumin and an excessive number of white blood cells. The eye-ground examination was negative. Spinal fluid examination was negative.

Electrocardiogram.—Rate 110; rhythm regular; spreading of the base of the R-spike suggested delay of conduction along a branch of the bundle; a-v conduction time was normal; there was no disturbance of the muscle balance. Evidence of myocardial degeneration, probably advanced, was present.

X-ray of the chest showed no special pulmonary findings but an interesting observation was made regarding the heart and aorta, as follows: "There is an atheromatous plaque in the aortic knob and a slight fullness in the region of the left auricle. The heart is enlarged, particularly to the left. Its transverse diameter is 15 cm.; while that of the chest is 27 cm."

The patient was very ill and stuporous almost from the beginning. Near the end of the illness pulmonary findings became a little more marked, that is, dulness increased at the right base posteriorly, breath sounds were harsh, and numerous râles were heard. The temperature averaged about 103° with sharp peaks; the pulse and respirations accordingly were raised. Death occurred on June 7.

Autopsy was delayed until the following day. Interest centered chiefly about the heart which weighed 350 gm. The pericardial sac contained a little excess of cloudy fluid and there was some evidence of acute inflammation. The muscle of the

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left ventricle was soft and pale. A ductus arteriosus was present and was filled with recent thrombus material which stopped abruptly at the aortic opening of the ductus but continued on the pulmonic side so that a large soft thrombotic mass 1.5 cm. in diameter was attached to the wall of the pulmonary artery and projected into the lumen of the vessel. At the point of attachment of the ductus to the aorta there was a hollowed-out depression measuring 1 cm. in diameter. At this point was a large calcified plaque. It was flat and disk-like with very small nodular projections.

The right lung contained a number of suppurative areas varying in size from a few millimeters to several centimeters. The uterus, tubes and ovaries were matted together by dense adhesions. The tubes were dilated and the lumen of the left was closed off at its point of entrance into the uterus and several places in its course. In other places it was filled with bloody exudate. The left ovary and part of the tube were necrotic and there was considerable fibrous tissue reaction about them.

The post-mortem diagnoses were: (1) Bacterial endocarditis of the ductus arteriosus and adjacent pulmonary artery, (2) Calcified plaque of the aorta at the point of entrance of the ductus arteriosus, (3) Acute fibrinous pericarditis, (4) Multiple pulmonary abscesses, right lung, (5) Chronic suppurative left oophoritis and salpingitis.

#### COMMENT

The diagnosis of patent ductus arteriosus frequently can be made by the presence of a "machinery" murmur and intense thrill in the pulmonary area and evidence of an exaggerated pulmonary area under the fluoroscope or on the x-ray plate. The absence of cyanosis and clubbing are negative points of importance in differentiating from congenital lesions of the pulmonary orifice. In the present case evidences of sepsis dominated the clinical picture and the murmur in the pulmonary area was considered to be of hemic origin. The calcified plaque of the aorta had a significance in this young woman which was not appreciated at the time.

A communication from Dr. M. E. Abbott, whose contributions to congenital heart disease are authoritative, informs me that in her series of 90 cases of patent ductus arteriosus calcific deposits at the aortic end of the ductus were observed in two cases, as follow. Murray<sup>1</sup> noted calcification of the wall of the aortic side of a patent and infected ductus in a patient aged 36 years, and White<sup>2</sup> recorded marked sclerosis and calcification at the aortic opening of a patent ductus arteriosus in a patient who attained the age of 66 years. However in White's case there was marked calcification of the remainder of the aorta. Abbott observes that the finding is probably more common than her series indicates. It is suggested therefore that in cases of suspected ductus arteriosus in young persons, in whom the presence of calcification from ordinary arteriosclerosis would be unlikely, roentgen-ray evidence of calcification in the arch of the aorta may be looked upon as a confirmatory sign.

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# Society Transactions

## AMERICAN HEART ASSOCIATION SEVENTH ANNUAL SCIENTIFIC SESSION

JUNE 9, 1931

The morning session was called to order by the President, Dr. Robert H. Halsey of New York, in the auditorium of the Institute for Mental Hygiene of the Pennsylvania Hospital, Philadelphia, Pa., at 9:40 o'clock. The following program was presented:

1. DR. R. L. HAMILTON, SAYRE, PA.—**Precordial Pain—Its Cause and Significance.** (Abstract of Dr. Hamilton's paper.)

The increasing incidence of anginal pain and of sudden death has focussed the attention of the public as well as of the physician on precordial pain. Two hundred case reports of patients with precordial pain associated with organic or functional cardiac disturbances were analyzed. In sifting out the cases 27 different extracardiac causes of pain were encountered. The cases with pain associated with cardiac disturbances could be separated into five groups: (1) those with relative coronary insufficiency, (2) those with aortic pain, (3) those with pain produced by a viscerosensory reflex, usually from the gall bladder, (4) those with acute pericarditis, and (5) those with pain associated with an increase in venous pressure.

The most common diagnoses were coronary occlusion and angina pectoris. The principal etiological factor was infection between the ages of thirty and forty years, hypertension between the ages of forty and fifty-five years, and arteriosclerosis in patients more than fifty-five years of age. The prognosis was uncertain, especially in the middle group, but in general was better in the younger patients and in the very old. There were more cases of organic heart disease in men than in women, although the incidence of hypertension was nearly the same in the two sexes, and the incidence of neuroses was higher in women. The study suggested that heredity, sedentary occupation with mental strain and possibly the use of alcohol and tobacco played a part in the production of precordial pain. The incidence of infections and of associated diseases agreed with the findings of other workers.

2. DR. FRED M. SMITH, IOWA CITY, IOWA.—**Presentation of Case.** (Abstract of Dr. Smith's presentation.)

Dr. Smith presented the case of a man, aged sixty years, who gave a characteristic history of angina pectoris. The distress began over the lower substernal region and was transmitted to the left shoulder and often down the left arm. It was invariably precipitated by exertion or excitement. He first came under the observation of Doctor Stroud three years ago shortly after the initial attack which lasted about thirty minutes. During this period he had experienced numerous attacks of varying intensity. There was a slight increase in the size of the heart. Otherwise



the cardiac findings were essentially negative. The blood pressure was well within normal range, and there was no history of hypertension. The blood Wassermann was negative. The urine likewise was negative.

The patient was of particular interest because of the relationship between angina pectoris and coronary occlusion. Each of these conditions was ordinarily associated with an advanced sclerosis of the coronary arteries. They probably represented different steps in the same pathological process and differed only in the extent of the functional impairment of the myocardium. Coronary occlusion might be regarded as a complication of coronary artery disease, and it was not surprising that it should occur during the course of or terminate in angina pectoris. The history of the sudden onset of a rather severe form of angina pectoris in this patient and the duration of the initial attack suggested a coronary occlusion. The electrocardiogram taken some time later showed suggestive changes in the T-wave which supported this possibility. It was generally known that coronary occlusion might precipitate an angina pectoris. This means of producing an angina was, however, probably far more common than was generally recognized. It was furthermore not improbable that minor forms of coronary closure were frequently overlooked during the course of angina pectoris.

3. DR. ALFRED FRIEDLANDER, CINCINNATI, OHIO.—**Electrocardiograms in Patients With Cardiovascular Lesions as Compared With Electrocardiograms in Cardiovascular Disease of Other Etiology.** (For original article, see page 15.)

4. DR. LEWIS A. CONNER, NEW YORK, N. Y.—**Presentation of Case.** (Abstract of Dr. Conner's presentation.)

Dr. Conner presented the case of a man of seventy years who for several years had had attacks of anginal pain of increasing frequency and severity. At first the attacks came on only on walking, later they appeared also with excitement, after eating and sometimes during the night. There had been no attacks that could be recognized as those of coronary thrombosis. The speaker discussed the case only from the standpoint of treatment. In his own experience treatment of effort angina by drugs and by rest had given such very disappointing results that he had been led to seek some other method of treatment. He called attention to the fact that different forms of physical effort vary greatly in their proneness to induce anginal pain; many patients who could not walk even a short distance without the appearance of pain were yet able to take other forms of active exercise, such as running upstairs or calisthenics, without such pain. In view of the evidence offered by Gross as to the pronounced tendency toward increased vascularization of the heart muscle in the middle and later years of life, it seemed rational to attempt to hasten the development of new coronary branches by the use of graded exercises, provided such exercises could be carried out without inducing pain. For the past two or three years he had been using such graded exercises, although at first very hesitatingly and cautiously. The early experiments had been sufficiently encouraging to warrant the systematic use of such exercises, and the results had thus far been highly satisfactory. Only a few cases, however, had been followed sufficiently long to know if the benefit was likely to be permanent. One case had been followed two years. At the time these exercises were started this man had been unable to walk at all because of the severe pain and had been confined to his room. After a month or two of graded exercises the pain had so far disappeared that he could resume active work, and for the past year he had been free from pain and actively engaged in his work as civil engineer. In several other cases there had been freedom from

pain for a number of months. He had never seen a case in which he thought harm had been done by the exercises. He had used the setting-up exercises of the Army, consisting of light, quick movements, limiting them at first to four or five minutes and having them done several times a day, preferably every two or three hours. It was important that they should be such as did not bring on pain, that they should not be done immediately after a meal and that they should be carried out in a comfortably warm room, in other words that the conditions likely to induce anginal pain be avoided as far as possible.

There was another, more serious aspect of these cases of effort angina, which was the likelihood sooner or later of an attack of thrombosis. If it was possible by graded exercises to increase the anastomotic circulation in the heart, it seemed reasonable to suppose that this increase might lessen materially the serious effects of such a closure if it should come.

The speaker said that the details of the method of treatment offered were by no means firmly established and could probably be improved upon, but he was quite convinced that if the problem were ever to be solved the solution would come from some method of development of the anastomotic circulation in the diseased coronaries.

5. DR. DREW LUTEN, ST. LOUIS, MO.—**Contributory Factors in Coronary Occlusion.** (For original article, see page 36.)

6. DR. GORDON E. HEIN, SAN FRANCISCO, CALIF.—**Presentation of Case.** (Abstract of Dr. Hein's presentation.)

Dr. Hein presented the record of a young man of twenty-nine years who had an attack which resembled one of coronary thrombosis and who died thirty-six hours later. The diagnoses suggested were: (1) coronary infarction; (2) rupture of the aorta, possibly secondary to aneurysm of the ascending aorta; and (3) occlusion of a large branch of the pulmonary artery. Autopsy revealed narrowing of the isthmus with dilatation proximal to this and a transverse tear 2 cm. long 6 cm. above the aortic cusps.

Dr. Hein discussed the recognition of coarctation of the aorta in those cases in which the diagnosis is not easy and commented on the relative frequency of rupture of the aorta in this condition.

7. DR. STEWART R. ROBERTS, ATLANTA, GA.—**Nervous and Mental Factors in Angina Pectoris.** (For original article, see page 21.)

The afternoon session was called to order at 2 o'clock, and the following program was presented:

8. DR. JOHN H. MUSSER, NEW ORLEANS, LA.—**The Familial Incidence of Coronary Thrombosis.** (For original article, see page 45.)

9. DR. DAVID RIESMAN, PHILADELPHIA, PA.—**Presentation of Cases.** (Abstract of Dr. Riesman's presentation.)

Dr. Riesman showed a little Italian girl of thirteen years who exhibited in a striking manner Broadbent's sign of retraction of the lower chest, laterally and posteriorly, as the result of adherent pericardium. The child had suffered for years from rheumatic pancarditis—both aortic and mitral valves were involved; the heart was greatly hypertrophied; retraction of the ribs had steadily increased during the

year and a half she had been under observation. When first admitted her tonsils had been found large and infected, the glands at the angles of the jaw and in the neck were likewise much enlarged. Despite her serious cardiac disease, she bore tonsillectomy under general anesthesia as well as a healthy child. The glands of the neck promptly diminished in size after the operation and soon could not be felt. Taking out the tonsils in this case was, of course, like shutting the stable door after the horse had been stolen.

Dr. Riesman passed around Broadbent's little book in which the sign known by his name was described.

The second patient was a colored man who had recently been admitted to the Philadelphia General Hospital in an advanced stage of circulatory decompensation. Under tapping and novasurol the signs of decompensation had rapidly disappeared. Dr. Riesman presented him as an example of nonvalvular heart disease. There was nothing in any way abnormal audible on auscultation of the heart; the blood pressure was about normal—it might have been higher previously, but of that there was no information; the Wassermann test was negative; there was no evidence of renal disease. The speaker discussed the nature of such cases of decompensation which evidently were due to muscular and not to valvular defect. He believed that coronary disease might be the basis of the cardiac myasthenia. At autopsy such cases showed no signs of inflammation. Hence the clinical term myocarditis was misapplied; he had coined the term "myocardosis" to designate the condition.

Dr. Riesman also spoke of the increasing frequency of myocardial failure since the onset of unemployment and hard times and was inclined to attribute it to food deficiency.

The ultimate cause of myocardial failure was probably chemical, whether faulty metabolism of lactic acid or something else was still undetermined.

Attention was called to the frequency with which hydrothorax is overlooked. The striking effects of novasurol were also pointed out.

# 10. DR. JOSEPH T. WEARN, CLEVELAND, OHIO.—The Relationship of the Thebesian Circulation to Coronary Occlusion. (Abstract of Dr. Wearn's paper.)

Correlation of clinical findings with the necropsy reports has shown many cases which revealed few signs or symptoms referable to the heart and yet whose coronary arteries were practically closed. Arteriosclerosis was the most common cause of the occlusion. Syphilitic aortitis, in some instances, resulted in the complete closure of both coronary orifices and in many instances occluded the opening of a single coronary artery.

These processes—arteriosclerosis and syphilitic aortitis—bring about a gradual occlusion of the coronary arteries, and in many instances they produce few, if any, distressing signs or symptoms of heart failure. Indeed, some escape detection during life.

Such cases are in distinct contrast to those where there is a sudden occlusion of a branch of a coronary. In these heart failure is usually the immediate result and death frequently follows.

When the coronary arteries are completely occluded either at their mouths by syphilis or in their main trunks by sclerosis, the hearts may carry on their work and eventually when examined they do not show infarction. These findings make it necessary to find another source of blood supply to the myocardium, and this blood supply must be sufficient to enable it to maintain a normal circulation.

Batson and Bellet<sup>1</sup> have suggested a reverse flow from the right auricle through the coronary sinus and great veins as a means of blood supply to the myocardium.

That there might, under the conditions of their experiments, be a slight back flow into the veins during auricular systole is quite possible. But their suggestion that the low pressure in the right auricle can maintain a circulation in the myocardium sufficient to enable it to keep up a normal blood pressure, is to me not acceptable.

Histologic studies<sup>2</sup> have shown direct communications between the Thebesian vessels in the ventricles and the capillaries of the myocardium. No valves have been found in the Thebesian vessels. The blood under ventricular pressure, therefore, has direct access to the capillary bed of the heart.

It is suggested that in many of the patients whose coronary arteries become occluded, the Thebesian vessels offer a channel of communication between the ventricles and the capillaries.

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#### 11. DR. JAMES B. HERRICK, CHICAGO, ILL.—Presentation of Cases. (Abstract of Dr. Herrick's paper.)

Dr. Herrick presented the following cases:

**CASE 1.** An adult woman after a prolonged stay in the hospital, with many weeks in bed, made a good recovery from what was clearly a moderately severe attack of coronary thrombosis.

**Comment:** Two points may be emphasized, the importance of rest in the treatment, and the difficulties in the way of diagnosis as well as of treatment when, as in this case, there were exaggerated nervous symptoms of a functional character.

**CASE 2.** A white man of forty-four years with a history of chancre at seventeen years, was suddenly overcome by pain in the chest, right shoulder, face, epigastrium. He was dizzy and for a few minutes may have been unconscious. Taken at once to a hospital, he complained of a dull ache in the precordium and between the shoulder blades. He was not dyspneic or cyanotic. The heart tones were faint, the pulse was just perceptible. There were many extrasystoles. On one day, for a few hours only, a pericardial friction sound was heard. The temperature rose to 100.6°. There were 11,200 leucocytes. An electrocardiogram taken on the ninth day showed QRS complexes of low amplitude and notched in all leads. The T-wave was inverted in Lead III. Three weeks later typical coronary waves were seen in Leads II and III. The diagnosis was acute coronary occlusion. It is now two years since the accident. He is able to do light work with only slight fatigue and slight shortness of breath. He complains at times of mild precordial distress and palpitation.

**Comment:** One may note the nearly complete functional recovery after rest. While syphilis in this case may have been a factor contributing to the occurrence of the thrombosis, no definite proof was afforded of relief from specific remedies.

One must be prepared to recognize cases of coronary thrombosis with mild or atypical symptoms. Often diagnosis must be made not on any one symptom but on the grouping of symptoms, the instrumental findings and the exclusion of other diseases. Of especial value in this case were the fever, leucocytosis, pericardial friction sound and the extrasystoles. The low voltage and notched curves were also suggestive. Still more significant was the fact that three weeks later the electrocardiogram showed further changes. The process was clearly one in which the myocardium was undergoing alterations presumably in the way of healing. The especial point to be stressed is that in these acute cases the tracings are not always fixed and unalterable. The diagnostic value of change in the electrocardiogram should not be overlooked.

12. DR. PAUL D. WHITE, BOSTON, MASS.—**The Prognosis of Angina Pectoris (500 Cases) and Coronary Thrombosis (200 Cases).** (For original article, see page 1.)
13. DR. EMANUEL LIBMAN, NEW YORK, N. Y.—**Presentation of Case.**

## DISCUSSION

DR. WOLFFE, Philadelphia, Pa.—Dr. Hamilton's paper is of great importance because of his clear observations. Numerous statistical studies have been reported, but it would be of great benefit to the students of angina pectoris if we were to have more studies of the character presented here this morning. The etiology of angina pectoris, as Dr. Hamilton pointed out, is still unknown although many theories have already been advanced. The clinical and pathological manifestations have been pointed out and are fairly well recognized. May we not draw some conclusions from the work already done? If one were to consider all these manifestations, as well as some of the known pathological lesions associated with this malady, a rather important conclusion would suggest itself. May not all the various etiological factors produce this symptom complex by a common *modus operandi*? May we not look upon angina pectoris as a reflex due to an imbalance of the two opposing parts of the autonomic nervous system, a parasympathetic and sympathetic imbalance (although even this nomenclature may have to be somewhat modified)? The symptoms and physical signs may depend greatly upon the preponderance of one or the other side of the autonomic nervous system. The drugs to be employed to check this dangerous and painful complex will also depend on the proper recognition of this disturbed balance. Dr. Hamilton clearly showed how the heart beat returned and the volume improved following the administration of epinephrin, yet Levine and his coworkers showed that epinephrin will in many cases precipitate an attack of angina pectoris. This has also been the experience of many clinicians. It is also a common experience that the same type of therapy given for a similar condition will improve one patient and aggravate the symptoms in another. May it not be well carefully to investigate symptoms and physical signs and see which side of the autonomic nervous system has the upper hand and direct treatment accordingly—using "inhibitor" drugs for the "accelerator" type and "accelerators" for the "inhibitor" types? This thought may be applied to many other diseases. The T-wave appears to be a very important guide provided we do not speak of it as a "coronary T-wave" but rather as a T-wave of sympathetic and parasympathetic imbalance.

DR. HAMILTON, Sayre, Pa.—With regard to Dr. Wolffe's observations with adrenalin I might say that not long ago I had a patient who I thought had a paroxysmal hypertension and gave him a little adrenalin to see whether or not I could bring out the symptoms. He developed such an intense coronary pain that for a few moments it seemed as though he might die.

DR. OPPENHEIMER, New York, N.Y.—Dr. Friedlander has mentioned incidentally the work of Dr. Master on certain electrocardiograms found in cases of hypertension, i.e., left axis deviation associated with inversion of the T-wave in Lead I, or sometimes in both Leads I and II. At the time of publication there was some doubt whether such T-wave changes were not due to coronary artery occlusion complicating hypertension. Since then I have had the opportunity of following a few such cases and seeing the hearts at necropsy, and have been convinced that such electrocardiographic changes may occur without coronary occlusion. For example, one patient with marked essential hypertension in whom these typical electrocardiographic changes persisted up to the day of his death, showed at necropsy an enormously

hypertrophied heart, weighing 1050 grams, and yet no coronary occlusion or myocardial infarction to account for his T-wave changes. Similarly electrocardiographic changes have been seen in instances of rheumatic aortic valvular disease, without finding coronary occlusion in the heart at post-mortem examination. So one may say that such inversions of the T-wave in the presence of left axis deviation do not necessarily mean coronary artery occlusion.

DR. PARDEE, New York, N. Y.—I should like to say a word about the relation of electrocardiographic abnormalities to mortality and to prognosis. In this table and in many other similar studies an effort has been made to decide whether or not certain peculiar features of the electrocardiogram have some relation to the length of time a patient is going to live. It seems to me that in order to have such a decision of any value, the figures must point overwhelmingly in one direction, that is, the percentage must be as high as 80 or 90, because there are so many other factors besides the electrocardiographic abnormality that must be taken into consideration in the prognosis. I do not feel that any of the percentages in Dr. Friedlander's tables indicate a definite seriousness of the observed physical sign. Electrocardiographic abnormalities are only a small part of the clinical picture, and I think that this is the reason that different authors, in attempting to estimate their importance, have found varying percentages and different trends. To me the figures would have to point much more strongly in one direction than do these before they would have prognostic significance.

DR. WOLFFE, Philadelphia, Pa.—Dr. Friedlander's paper again proves that there is no such thing as a pathognomonic coronary T-wave. This type of T deformity may be produced as have already pointed out if the animal's autonomic mechanism is disturbed by administering certain drugs and particularly certain hormones. A coronary insult may also produce a similar T-wave, but apparently due to a similar mechanism. It seems that if the coronary insult is superficial it involves one side of the balance, while if deep, the other.

The T-wave promises to be a very important index in diagnosis and treatment in every branch of medicine. It would be difficult in these few minutes to offer enough proof even to suggest changing deeply rooted ideas. I can nevertheless assure you that we have records showing typical coronary T-waves in individuals with a perfectly normal cardiovascular system as far as organic disease is concerned. In the dog we can depress the T-wave by the use of the substance I previously mentioned as desympatone and bring it up again by administering epinephrine.

I may say in conclusion that those working with the electrocardiograph should keep in mind parasympathetic and sympathetic imbalance, whether due to coronary disease, a blow over the chest or epigastrium, a sensitized nervous system, or gall bladder disease; for all may produce changes of the T-wave, and therefore a diagnosis and prognosis should not be based entirely upon this finding.

DR. MARVIN, New Haven, Conn.—Dr. Conner has spoken of the work of Gross as indicating that as an individual grows older he develops fairly abundant anastomoses between the branches of the coronary arteries. It seems to me of some importance to indicate that this view of Gross' is by no means generally accepted. I have discussed the matter with some pathologists who have no hesitation in regarding it as being incorrect, unsound in theory and untrue in fact, and they point out that if this is true of the heart, it is peculiar to the heart muscle, that such processes do not occur in other tissues of the body as the individual grows older, that this process is a development of an abundant anastomosis of new, young and growing tissue and not one that is undergoing degenerative processes. Those of you who have seen the illustrations in Gross' book will agree that they

are apparently conclusive, but there is an alternate explanation which seems to some of us acceptable. It is this: in the younger hearts the arteries are more elastic, either they do not permit the injection medium to enter them because they are closed by virtue of their elasticity, or, having permitted the injection medium to enter, they probably squeeze it out into the larger vessels so that if x-rays of such hearts are taken no anastomoses are demonstrated. As the hearts grow older the arteries become more sclerotic, less elastic, permit the injection fluid to enter, and the apparent anastomoses are shown which may actually have been present for many years.

DR. LIBMAN, New York, N. Y.—There is no reason why a collateral circulation should not gradually develop, in view of the studies of Kusnetzowsky and others that the coronary arteries begin to show changes from birth on.

DR. THAYER, Baltimore, Md.—I have been very much interested in what Dr. Conner has said. I have been much interested in the subject in general, and it seems to me that there are a good many sides to it. In the first place, if one wants to help an individual who has angina of effort, such as the patient of Dr. Conner, it seems to me the first thing one can do is to let the patient know what is the matter with him. That does not mean to tell him he has angina, of course, that would be a stupid thing to do, but it does mean making friends with the man and telling him as well as you can what you think is the matter with his circulation. Then it seems to me the next thing to do is to encourage him to feel that he can do certain things to improve his circulation very much. If I can, I usually put him to bed for a certain period but this is never done without combining it with massage. Now generally when it is done, after a certain length of time the patient becomes greatly encouraged to find that he is going through his days without the pain, and then, after a certain length of time, I always begin—perhaps not quite so vigorously as Dr. Conner has—but I always begin with the setting-up exercises that were used in the U. S. General Hospital No. 9 for the treatment of the so-called effort syndrome. I have often been quite amazed at the improvement one may get. I have in mind the case of a man of seventy who had been having five or six attacks every night, besides great difficulty during the day. As he would not go to the hospital, he was put to bed at home and later was put on the graded exercises. The old fellow went a year or two actually without pain and has been able to continue at his work for three or four years. He learned, as these people do, that he could get rid of his pains to a very considerable extent if he would regulate his life. You can talk to a man for days and accomplish nothing, but a demonstration teaches him how to live just as Weir Mitchell taught neurotics how to live by giving them a rest cure.

DR. LEE, Washington, D. C.—May I ask Dr. Conner if he includes in these exercises cases of previous coronary thrombosis, and if so, after what general period of rest time?

DR. MCCULLOCH, Saint Louis, Mo.—Dr. Conner's presentation of this case has brought out some ideas that are extremely important, particularly the differentiation between sustained effort and the slight effort of short duration in producing pain. It has been pointed out recently by Bramwell and Ellis\* that individuals with normal hearts may respond to different forms of exercise in various ways. As a result of their studies on runners in Olympic Games they state that sprinters who run relatively short distances can do so without breathing or using the heart during the time they are undergoing this form of exercise; whereas, a runner who does sustained effort, for example, during a marathon race will have a very different re-

\*Quarterly J. Med. 24: 329, 1931.

sponse to this exercise; that is, the respiration, circulation and heart muscle must be so conditioned as to carry on during the longer period of excessive effort. The circulatory conditions must be such that the heart muscle receives an adequate supply of food material and an adequate removal of waste during this period. It may be that this is of some importance in allowing exercise for such patients as Dr. Conner describes because the circulatory needs of a patient with coronary thrombosis or with interference in coronary flow from other causes may be comparable to the person undergoing a marathon race; whereas, the patient with obstructed flow through a heart valve may be comparable to a person undergoing a short sprinting-exercise. It seems to me, therefore, that the differentiation between these two forms of exercise is important and should be kept in mind as Dr. Conner has pointed out. The explanation that might be offered for the difference in the response between the two exercises is that the reserve in the heart as well as the skeletal muscle cells may be used up completely in sustained effort without adequate provision for replenishment of materials or removal of waste through the injured coronary circulation.

DR. CONNER, New York, N. Y.—I do not feel qualified at all to discuss the point raised by Dr. Marvin concerning Gross' conclusions. I know there is a difference of opinion and I am quite prepared to believe that such increase in vascularization may not be a universal thing, but it seems to me one cannot deny that the heart is capable of developing an elaborate anastomotic supply, otherwise I do not see how one can explain these cases that one sees occasionally, such as those that Dr. Wearn has reported upon, of complete or almost complete occlusion of both coronaries and yet with the maintenance of fairly good health. There must be an elaborate anastomotic supply, as well as the increased use of the Thebesian vessels I should think. I am much interested to hear what Dr. Thayer has to say about the use of exercises. I have not attempted to discuss the many collateral things in the treatment, but, of course, I agree fully with Dr. Thayer as to the need of having the patients—if they are intelligent at all—understand the circumstances and understand the need of living within the limits of their capacity; but I am glad to know that he has been trying to work out in the same way that I have this matter of exercise. I neglected to say that I have felt that the selection of suitable cases was very important, and at the beginning I should not have thought that this man of seventy with evident myocardial change was a very suitable case, but as I have gone on, I have come to feel, apparently as Dr. Thayer feels, that even cases that have definite and serious myocardial damage can still be benefited by such exercise. To answer Dr. Lee's question, I have not used the exercise at all in those people who have had definite coronary thrombosis and who have the after-pain. I do not quite know the significance of the pains that come after a coronary thrombosis. I have been inclined to associate them with the actual damage done by the thrombosis. It is possible, I suppose, that they may be merely anginal pains from some other arterial branch or branches that are sclerotic and are beginning to give their symptoms, but usually these post-thrombotic pains do not have quite the typical behavior of those of effort angina.

DR. LIBMAN, NEW YORK, N. Y.—In connection with Dr. Luten's discussion of the subject of pain, I shall probably have time to indicate this afternoon that all of the proposed theories have truth in them but that they apply to different types of cases. I should like to emphasize the subject of contributory factors in coronary thrombosis. In 1919 I pointed out that patients who suffer from coronary thrombosis may have a history of thrombosis in veins, and are liable to develop thromboses in the arteries of the lower extremities and of the brain, often insidiously. I indicated that there was something present apart from the disease of the vessel wall—especially as thrombosis may occur in a coronary artery slightly diseased and



not in those showing marked changes. This condition I have since termed "thrombophilia." Recently I found that a writer by the name of Mandel used the term "thrombophilic" for the same purpose (original paper not yet located). It is important I believe to seek along the line of metabolic disturbances for an explanation of the larger number of cases of coronary thrombosis. If one studies their histories and also the family histories, one finds many conditions present which we group as gout, typical or atypical, or as "goutiness." In going over my records I find almost the same disturbances present as Allbutt found in his elaborate studies of families in Leeds, carried on for a long time. It is interesting to find that von Recklinghausen stated (not specifically in relation to the coronary arteries) that there exists a tendency to thrombosis in certain individuals, apart from circulatory factors, and that this is associated with metabolic disturbances such as gout and diabetes. A study of this subject should give us important clues in treatment and in prevention. I might add parenthetically that I am of the opinion that the factors that predispose to coronary thrombosis also play a rôle in the development of atherosclerosis of the coronary (and other) arteries and of the nerve type of so-called angina pectoris. This would explain why we may encounter these conditions, associated and separately.

DR. KATZ, Chicago, Ill.—In regard to Dr. Luten's paper, emphasis was laid on the fact that spasm or constriction occurs in the coronary arteries clinically. The idea was based on the work of Anrep and Segall, which is contradicted in part by Wiggers. Anrep and Segall computed the coronary inflow from the flow from the coronary sinus on the assumption that 60 per cent of the total inflow was measured by the coronary outflow, a fact which Wearn has questioned. I therefore wish to point out that there is no clear evidence that coronary spasm or constriction occurs, or, at least, that it is of any significance clinically in causing impediment to coronary flow. All the changes met with in coronary flow, aside from those caused by organic lesions, can be readily accounted for by changes in blood pressure—especially the diastolic. Anrep has shown clearly that the most important determining factor for coronary flow is the aortic blood pressure. Any marked lowering of the blood pressure will cause an ischemia of the heart and thus cause pain and other symptoms, and may, as in a case which Dr. Wallace and I reported, lead to death with the typical signs of coronary occlusion. There is no need to assume that coronary spasm occurs until direct evidence is brought forward for its occurrence, or until proof is given that changes in blood pressure cannot explain all the effects attributed to spasm.

DR. LUTEN, Saint Louis, Mo.—I am very much obliged to Dr. Libman. His remarks go further back to ultimate causes than mine. Diabetes, of course, is particularly associated with coronary sclerosis in the first place, but even so, certain patients with coronary sclerosis experience occasions of low diastolic pressure without occlusion while others get occlusion under such circumstances. Dr. Libman's explanation would tend to account for this difference. I do not mean to imply that gastrointestinal reflexes in causing possible coronary constriction are the principal contributory factors in occlusion. Most cases of occlusion occur at night, particularly in the early hours of the morning, when diastolic pressure is low. I was merely offering evidence that such reflexes may constitute additional contributory factors. One bit of collateral evidence lies in the work of Pearey and Howard. They produced extrasystoles and changes in the ventricular complex by visceral stimulation. It is common clinical experience, of course, for disturbances in the gastrointestinal tract to produce extrasystoles. Now, Pearey and Howard are convinced that this is not due to pressure but to a reflex.

DR. THAYER, Baltimore, Md.—I should like to ask Dr. Hein what was the condition of the aorta in the region of the rupture, whether there were marked degenerative changes. As I understand there was no syphilis. It would be rather a striking thing if the aorta had ruptured in the absence of obvious anatomical change near the point of rupture.

DR. HEIN, San Francisco, Calif.—The aortic wall was smooth except just at the point of rupture. It was decidedly thin; there was no arteriosclerosis of the ascending aorta and no abnormality of the valves. Congenital weakness of the aorta may be one of the reasons for rupture, and in such cases apparently the rupture is within the first 6 or 8 cm. of the ascending aorta. We all know that coronary occlusion may occur without pain, but we are beginning to be a little suspicious of our diagnosis in those cases in which pain is not present. In the last two cases in which we made the diagnosis of coronary infarction in the absence of pain, our diagnosis was wrong.

DR. THAYER, Baltimore, Md.—I should like to ask Dr. Roberts if he is not able sometimes to extract from a colored patient, in whom he suspects angina, something which confirms his suspicions: a fairly clear story of angina? I do not know that I can remember ever getting it myself, but I think since we have been very much interested in the subject in Baltimore we have been able, when we suspected it from the general story, to get something in that direction. I remember one woman with coronary thrombosis; there was not one word in her history as written that suggested pain, but quite accidentally I happened to see the student who met the patient as she came to the out-patient department; he told me that she had complained of a toothache-like pain in her left forearm. And now and then I think one can get the equivalent of the story of angina from the patient. But *angor animi* and the clear objective description of the pains, one does not get.

DR. MARVIN, New Haven, Conn.—I should like to ask one general question which I hope several of the speakers will answer, and that is what their experience has been with the use of the xanthine derivatives, namely metaphyllin, theocin and theobromine, in the treatment of this condition. My own experience has been most discouraging; I am not satisfied that I have ever seen any benefit follow the use of any of these.

DR. OPPENHEIMER, New York, N. Y.—May I call attention to a certain parallelism between exophthalmic goiter and angina pectoris from the point of view of the rôle of nervous and mental influences as an etiological factor? I happen to be connected with a New York hospital which is in a neighborhood in which there has been a large influx of negro population and of about 100,000 Porto Ricans. Formerly Graves' syndrome was considered rare in the negroes in New York City, but of late such cases have ceased to be rare among the negroes, and we have even had two negroes with exophthalmic goiter in the ward at the same time. Graves' syndrome has also been observed recently in a few Porto Rican women. In both groups, negro and Porto Rican, I am under the impression that industrialization under urban conditions is responsible for the apparent increase of exophthalmic goiter. Is it not the instability of the whole nervous system, more particularly, however, of the autonomic nervous system, which is an etiologic factor in the apparent increase of Graves' syndrome and also of angina pectoris in the urban population? I should like to ask Dr. Roberts whether he has noted Graves' disease in the negro population in his neighborhood.

DR. CONNER, New York, N. Y.—I must say a few words about the interesting paper of Dr. Roberts', even though we may be a few minutes late. Almost the finest thing that comes from these meetings of ours are these frank and full dis-

cussions, and we must all have felt deeply the effect of Dr. Roberts' wise presentation of this whole subject. It is extraordinary that such differences as he points out should occur in the different races, but I have no doubt they do occur, although they are perhaps not quite so positive as we now think.

Now to go back to the question of the great increase in angina and in coronary thrombosis—I have no way of knowing, I do not think anybody knows, the real situation. We get the impression that they have increased and it may well be so, because we have had a great admixture of races and great changes in our civilization; but I venture to say that Heberden, when he first saw these cases and described them so beautifully, must have wondered, since no one had described them before, if the disease was not greatly on the increase, and if such increase was not a result of the strain and stress of life in 1768 as compared with that of a century before.

Much of the apparent increase recently must be ascribed, I think, to the fact that these conditions are now so widely recognized both in the profession and in the laity.

DR. HALSEY, New York, N. Y.—By way of proof of the rarity of the disease in early days I might state that the records in New York City would indicate that no death occurred from heart disease from 1804 to 1808.

DR. ROBERTS, Atlanta, Ga.—To begin with Dr. Marvin's question first I agree with the intimation in his question.

To answer Dr. Oppenheimer I think I have seen only one case of exophthalmic hyperthyroidism in a pure African. One should distinguish between the pure African and the mulatto—there is a vast difference, as Dublin, in his statistics shows, in regard to their susceptibility to disease. I think your point is well taken, and that as the negro turns from the quiet country districts to the city with its industrialism we shall see the development of diseases in him that we have not heretofore seen. I do see occasional exophthalmic hyperthyroidism in mulattoes and, strange to say, adenomatous hyperthyroidism in my experience is particularly rare in the full-blooded African.

In regard to Dr. Thayer's point, I distinguished carefully in my remarks between the anginal symptoms of coronary thrombosis and angina as we know it without thrombosis or evidence of lues. We may have been not so thorough as we might in getting the history. A negro is an individual from whom it is very difficult to extract a correct history. But I certainly want to disagree with the statements that the negro is not as susceptible to pain as a white. In my experience he is more susceptible to pain than the white. But the point in my mind is that while he has a very well developed susceptibility to pain and sensitivity to pain he is lacking in the ability to worry unpleasantly. I was careful not to say that anginal pain does not occur in the full-blooded African, but to say only that we had not seen it. Such pain does occur in association with luetic aortitis. Although statistics are so unsatisfactory, I think the impression prevails, probably correctly, that angina is on the increase. I am sure that I have seen more cases of angina during the Florida "boom" and subsequent to its collapse than I ever saw before, and I think angina has been rather more prominent since a famous day in November, 1929, in New York City than it was before.

DR. RABINOWITZ, Brooklyn, N. Y.—The observation of Dr. Musser that in coronary disease the next generation suffers at a younger age is also borne out in the studies of cancer families that the cancer will occur at a much earlier age than it did in the preceding generation. The same observation has been made in cases of apoplexy. I have had an instance where the son died of an apoplectic stroke two years before the father.

DR. CONNER, New York, N. Y.—Mr. Chairman, speaking of arteriosclerosis, not just what Dr. Musser was emphasizing of course, I cannot resist the temptation to say that I think the habit of speaking of *general* arteriosclerosis has done more to confuse us and to cloud our understanding of the arteriosclerotic process than anything I know of, because arteriosclerosis is usually not general. It may be so ultimately in old age or with a long-standing hypertension, but arteriosclerosis—and you find such evidence all through the literature on the subject—is usually a local thing through all its earlier stages. Usually, too, it involves certain of the viscera, apparently often chiefly one, for a long while almost to the exclusion of the others and certainly often to the exclusion of the peripheral arteries. I do not know of anything more misleading than to attempt to appraise the state of the arterial system as a whole by running over a few peripheral arteries and judging it by their normal state or by their changes. It seems to me that it ought to be emphasized that arteriosclerosis is a focal thing to begin with, that in the viscera it often begins in very early life and may remain, as I have said, in one or a few viscera for a long time without any general involvement at all. Then I think with that conception we can understand how it is that these people at 35 or 38 or 40 years so often have their coronary attacks, just as others have cerebral attacks, and still others develop changes in the renal arteries at an unusually early age.

DR. KATZ, Chicago, Ill.—I should like to ask Dr. Wearn how the adjustments take place in the Thebesian vessels, whether this requires time, or whether the change occurs at the time the patient has a coronary occlusion.

DR. RABINOWITZ, Brooklyn, N. Y.—Has Dr. Wearn found greater enlargement of the thebesian vessels in cases of coronary occlusion than in apparently normal hearts?

DR. WOLFERTH, Philadelphia, Pa.—There are one or two points that might be raised here I think. Dr. Batson and Dr. Bellet, in maintaining a venous pressure at the normal level, were able to get particles of graphite deep into the coronary venous channels. Now, the only conclusion one can come to is that these particles had gotten down there by a reversal of flow, under the conditions of their experiments, which were of course, admittedly highly artificial, but they did get there, and occlusion of coronary arteries also produces an artificial condition. Now in the coronary arteries, when they are occluded, we have two sets of channels, coronary venous channels and the Thebesian vessels. It seems to me that either one of these might function as the source of the blood and the other for the return of the blood; it might be one, or it might be the other. Now if one considers this problem from the point of view of the dynamics of the heart, it has always been difficult for me to understand how blood would get in through the Thebesian vessels to nourish the heart. Dr. Wearn dismisses the work of Dr. Batson and Dr. Bellet as offering an unlikely explanation of this, but I should be very much interested to hear what pressure differences he believes develop in the ventricles which are superior to those which may arise from the auricle to get blood into the myocardium. Certainly, after systole begins one would think that the pressure within the myocardium itself would be at least equal to that of the intraventricular content, which would seem to me to be not a very favorable dynamic set-up for blood to enter through the thebesian vessels.

DR. WEARN, Cleveland, Ohio.—I have been asked a great many questions that I cannot answer. So far as I know, the answers to most of them are not known at the present time. Dr. Katz asked if there is a sudden change in the Thebesian vessels when they take over the function of the coronary arteries. The answer to his question would require knowledge of the size of the vessels before and after death.

I know of no way of getting such information. Even if one could look into the chambers of an intact heart the Thebesian vessels could not be seen. Their openings are usually buried beneath the trabeculae in the walls of the chambers. The fact is, if facts can be arrived at by deduction, that in the two cases cited, the thebesian vessels were the only channels by which the myocardium could get its blood supply under sufficient pressure to maintain it.

Now do the Thebesian vessels grow larger? Again I do not know. I do not know of any way of finding out, because you have not got them beforehand or afterward. They vary in size tremendously, from some with an opening of half a millimeter to those that are almost microscopic. You cannot see some of the openings and yet in injecting the hearts, one sees the dye ooze out through these particular places.

Some one else asked, "What blood pressure can the Thebesian circulation maintain?" I submit the two experiments to you, the heart of the woman with the luetic aortitis and that of the sailor, both of whom had complete closure of their coronary arteries and who had blood pressure enough to work and earn a living. The sailor could pull a rope on a boat and carry an armful of awning rods up a stepladder and put them up. That is sufficient, I should think, to show that the Thebesian circulation can maintain a normal blood pressure.

Dr. Wolferth's question brings up points on which opinions differ. Batson and Bellet's experiments have shown the presence of particles, injected into the femoral vein, in the cardiac veins. They believe that the particles got into the veins as a result of back flow from the right auricle, and from this evidence they conclude that back flow through the veins may furnish blood supply to the heart muscle.

I shall not attempt to explain how their particles got into the heart veins, but their conclusions are not acceptable to me. Their claims rest on a blood supply to the heart muscle, supported by pressure developed in the right auricle. The right auricle is capable of maintaining only a very low pressure.

The Thebesian vessels, on the other hand, open directly from the ventricular walls, and blood entering them would be under full ventricular systolic pressure. I have shown you actual histological sections which prove that the thebesian vessels open directly into the capillary bed. In other words they offer more direct channels to the capillaries than do the coronary arteries.

DR. KATZ, Chicago, Ill.—What was found at the autopsy in those cases of angina pectoris that died?

DR. LUTEN, Saint Louis, Mo.—May I ask Dr. White if he follows a more or less invariable rule as to the length of time he keeps a patient in bed after occlusion, even though all the evidence may indicate that the occlusion was in a small artery?

DR. ROBEX, Boston, Mass.—Is it not possible that some, perhaps many, of the more severe attacks of angina pectoris are due to thrombosis occurring in the finest branches of the coronary artery? The attacks are not severe enough to cause pericarditis, leucocytosis or even mild collapse. We know from hearts injected by Louis Gross and others that many of the old hearts show a great diminution in the finer branches of the coronary tree and they have probably become thrombosed. It is right to say that patients die of angina pectoris? Is not angina pectoris merely a symptom of some other condition?

DR. TALLEY, Philadelphia, Pa.—I have been interested in Dr. White's mention of respiratory difficulty without pain. A recent patient had no pain, but sudden great difficulty in respiration with leucocytosis, fever, characteristic electrocardiogram and later attacks of pulmonary edema. Even after two months on one floor, on two occasions one flight of stairs brought on attacks of acute pulmonary edema

that almost ended his existence. It was necessary to keep him on one floor for six months before he could do one flight with comfort. Since then he leads a comfortable but somewhat restricted existence.

DR. MORRISON, Boston, Mass.—I should like to ask if the degree of fall in blood pressure in acute coronary occlusion is of any prognostic value.

DR. MCGUIRE, Cincinnati, Ohio.—Have you any theory regarding the mechanism of the transient hyperglycemia which one finds following coronary occlusion? Have you observed a similar rise in the sugar content of the blood in cases of angina pectoris in which you believed that the coronary arteries were not occluded?

DR. WHITE, Boston, Mass.—Some of these are hard questions. As to the post-mortem examinations in our cases proved not to have coronary thrombosis, we have sometimes been astonished by the small amount of coronary disease or obstruction. Some of the patients, however, who died during an attack of angina pectoris had apparently good heart muscle with fair coronary arteries, and it is a mystery why they should have died.

Dr. Robey asked the question, "Do patients actually die of angina pectoris?" They die during an attack but we do not know what the mechanism of death is as yet; it is an interesting problem to be solved some day, but it is a considerable mystery. The death is not, apparently, like that of the Adams-Stokes syndrome with loss of consciousness and convulsions. Patients with angina pectoris die more quickly than that; they do not continue to live and have convulsions but they die at once. Why they die is a question that has not been answered; at least they die during attacks of angina pectoris.

As to whether smaller attacks of coronary thrombosis may occur to explain some of the severer attacks of angina pectoris, I do not think we can answer that. It is probable that minor thromboses can occur without reactions of fever and leucocytosis of any important degree, but generally it is easy to distinguish between the two, that is between angina pectoris and coronary thrombosis.

The length of time that I am accustomed to keep patients in bed after attacks of coronary thrombosis in the absence of any unfavorable signs or symptoms is a minimum of three weeks; if they have any unfavorable signs or symptoms, I require a longer rest in bed, sometimes months. We cannot be too careful and many people feel that three weeks are rather a short time. This depends on the individual case. There must be a long interval of convalescence; probably a few months of almost absolute rest at the beginning is a wise procedure if we want to establish a firm scar. I dare say that my minimum of three weeks may seem short, but some of my patients who are doing very well and who have survived for many years went through the relatively short period of absolute rest of two to three weeks followed by a convalescent period of some time after that before returning to moderate activity. Too long in bed is bad for the morale.

Diabetes was not common in my series, although it is occasionally found with angina pectoris; if we take a group of diabetic patients, we will find that angina pectoris is fairly common among them but diabetes is not correspondingly so common in groups of angina pectoris or of coronary thrombosis. I have little or no knowledge of the blood sugar content during coronary thrombosis.

The degree of fall in blood pressure is probably of some importance in cases of coronary thrombosis. It is of immediate importance, if extreme, in some patients who die very soon after the attack. A very low blood pressure lasting for weeks I think we may consider a bad prognostic sign, but many of my patients who survived for years had a considerable drop in pressure at first with a return to normal after a few hours or days.

## Book Review

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HERZ - UND KREISLAUFINSUFFIZIENZ. EIN KURZES SYSTEM DER STÖRUNGEN IM KREISLAUFAPPARAT. By Dr. K. F. Wenekebach. EM. Vorstand der 1. Medizinischen Universitätsklinik, Wien. 120 Seiten. Mit 7 Abbildungen. Dresden und Leipzig. Verlag von Theodor Steinkopf, 1931.

In view of the ever increasing mass of medical literature, it is quite proper to inquire whether a particular new publication is justified and will fulfill a need. If one applies this test to the admirable monograph by Wenekebach, one may answer the question unequivocally in the affirmative. It is necessary for teachers of medicine to present the results of laboratory investigations and their clinical scientific observations in such a form that he who runs (i.e., the practitioner) *will* read, understand and apply the new knowledge in his practice. Wenekebach has had this objective constantly before him and has reviewed the recent advances made in the clinical science of the circulation in an admirably simple way. It is noteworthy that he has been willing to follow the trend of the times in cardiovascular disorders and turn his attention from arrhythmias which were the main subject of the brilliant investigations of his earlier career to the hydrodynamics and mechanics of the circulation as a subject of contemporary interest with which the general practitioner has not as yet familiarized himself. Moreover, his viewpoint has been broad, his critical judgment excellent, and in his references to the literature he has done justice to the English, American, Dutch and Belgian workers in this field.

The monograph opens with an important introduction on the effects of local obstruction or interference with the blood stream, and a consideration of the reasons for the violent opposition of James Mackenzie to the "back-pressure" theory. Following this, the dynamic laws of the heart are discussed, and here a more elaborate exposition, even at the expense of more space, along the lines of Starling's Linaere lecture on the "Law of the Heart" would have helped to elucidate this rather difficult subject.

The subject matter of the monograph proper is divided into two main parts, both dealing with the laws of cardiac and circulatory insufficiency. In the first part are described the hydro-mechanic and dynamic consequences of various obstructions to the circulation, "*Ceteris Paribus*," i.e., other conditions, however, remaining the same; whereas in the second part entitled "*Ceteris non Paribus*," those factors are discussed which may alter or entirely change the events in the mechanism of the

circulation described in the first part—irrespective of whether such factors are helpful or detrimental to the circulation.

In the first part Wenckebach discusses disturbances of circulation of cardiac origin, including left heart failure, stasis in the pulmonary circulation, disturbance of the right side of the heart such as right heart failure, reciprocal relation of pulmonary congestion and hepatic congestion, reciprocal action of hepatic and renal congestion, tricuspid insufficiency, auricular fibrillation, the type of stasis due to pericardial disease, and circulatory disturbance resulting from equal damage to both sides of the heart. Then under the general topic of obstruction in the greater circulation, Wenckebach takes up the involvement of the large veins, and of the smaller and smallest veins, the phenomena of collapse and of shock, the capillaries, the arterial system including blood pressure, hypotension, hypertension, Hochdruckstauung (congestive hypertension) of Sahli, Stauungshochdruck, Heberden's angina pectoris, coronary circulation, and the reciprocal action of aortic and pulmonary congestion.

The second part of the monograph, with its caption, "*Ceteris non Paribus*," is devoted to a discussion of other factors which may modify the dynamics of the circulation previously described. The following are among the subjects treated: mechanical aids to the circulation, water exchange, metabolism, edema, metabolism and circulatory insufficiency, minute volume, stroke volume, oxygen debt, blood volume, short circuits in the circulation, velocity of circulation and cyanosis, cardiac rate and rhythm, digitalis therapy, dyspnea and its relation to the respiratory centre.

In one word, the book is a review of the contemporary views on the circulation and circulatory failure, written for advanced students and practitioners by an investigator and teacher of medicine who has himself taken an active part in the astonishing progress made in the study of the heart from the time when the chief interest was concentrated in the arrhythmias to the present period when the dynamics of the circulation as a whole appears to hold the centre of the stage. In this work Wenckebach has tried to bridge the great gap between the clinician and the experimenter, and believes the two may meet and by cooperation may make still further contributions to science, to the benefit of the practice of medicine.

B. S. O.



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## Original Communications

### CONGENITAL MEDIAL SCLEROSIS OF THE CORONARY ARTERY\*

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THAT medial sclerosis was to be clearly differentiated from atheromatosis of the intima, was recognized by Virchow,<sup>1, 2</sup> who described it as most frequently found in the peripheral arteries; but nevertheless it was included in the description of arteriosclerosis by Oberndorfer,<sup>3</sup> Jores,<sup>4</sup> Aschoff,<sup>5</sup> Kaufmann,<sup>6</sup> and Saltykow.<sup>7</sup> However, it was Mönkeberg<sup>8, 9, 10</sup> and Marchand,<sup>11</sup> who emphasized pure calcification of the media as an independent condition. These changes were also found to be present in the large arteries and coronaries, even in infants following infection.<sup>12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24</sup> The literature on the occurrence of spontaneous arteriosclerotic changes in the arteries of rabbits has been summarized by Newburgh and Clarkson,<sup>25</sup> and by Nuzum, Elliot, Evans, and Priest,<sup>26</sup> who described one type consisting of necrosis and calcification which appeared to affect the media. In the attempt to produce experimental arteriosclerosis, changes in the media have been reported by numerous workers using various methods, such as high protein and fat diets, adrenalin, pituitrin, cholesterol, uranium, alcohol and potassium iodide;<sup>25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 66</sup> also the discovery of irradiated ergosterol was soon followed by the description of medial calcification in animals after administration of large doses of this substance.<sup>43, 44, 45, 46, 47, 48, 49, 50, 67</sup> Pathological changes such as these have been reported in infants and newborn babies,<sup>18, 19, 51, 52, 53</sup> and some of them bear a sufficiently close similarity to the case herein reported to warrant reviewing.

McMicheal<sup>52</sup> described the case of a child eighteen months old, dying of thrombosis of the superior mesenteric artery, who also showed fibrous

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changes in the coronary arteries of the heart. This case was a gentile; family history including Wassermann reactions of both parents was negative. The infant had had no previous illness, and the terminal illness was ushered in by fever and mild gastrointestinal disturbance. At autopsy the heart was not found to be enlarged, but the coronaries were thickened and dense. Upon section they showed great connective tissue proliferation external to the elastic lamina with narrowing of the lumen; this condition was not present in the smaller arterioles. In the heart wall there was a loss of muscle tissue with replacement by fibrous tissue. Thrombo-angiitis obliterans and periarteritis nodosa were excluded because of the complete absence of any involvement of the adventitia. Although there was evidence of tuberculous infection in this case, it was not considered as an etiological factor, and the process was regarded as an endarteritis due to acute or subacute infection of an unknown nature.

Hughes and Perry<sup>53</sup> report a case of a child seven weeks old who died suddenly and at autopsy revealed marked thickening and tortuosity of the coronary arteries, while the rest of the heart appeared normal. There was intimal thickening composed of loosely arranged fibrous connective tissue, and the media was almost completely calcified, with only very broken fragments of muscle fibers, while the adventitia showed some increase in fibrous tissue. This change was also confined to the large arteries, while the arterioles were normal. The family history was negative, except for an attack of influenza in the mother during her pregnancy. Her Wassermann reaction was negative. Our opinion is that this was a case of primary pathology in the media, probably due to intrauterine influenza, similar to those cases reported by Wiesel.<sup>20, 21, 22, 23, 24</sup> Durante's<sup>51</sup> case was a premature child, fifteen days old, who died of acute peritonitis following an umbilical infection. The etiology in this case cannot be determined because of the lack of information regarding the parents, but syphilis, tuberculosis or alcohol might be factors. Histological examination revealed the myocardium to be normal, but there were lesions of all degrees, from granular degeneration to well-formed calcareous plaque, in the inner third of the media of the pulmonary artery. The external tunic was normal and the internal tunic probably became detached spontaneously after death. In the less severely affected regions there was a granular condition of the tissue, the cells of which stained diffusely and were less clearly separated from each other. The nuclei stained well but a granular substance deposited in the protoplasm or in the interstitial tissue masked the outline of these cells which appeared to be degenerating and had lost some of their affinity for stains. At the points where the lesion was more advanced, the tissue was infiltrated with masses which had an irregular outline and either remained unstained or were stained pale yellow with picrocarmine, and dark violet with hematoxylin, and

yellow with picric acid. These masses were insoluble in ether and in some places replaced the muscle cells. It was impossible to determine whether they were due to a transformation of the cellular elements or whether they had been deposited between the cells, although Durante is inclined to the latter hypothesis. In the slightly affected regions the lesion was clearly limited to the internal third of the media, and at the points at which the lesion reached and projected into the interior of the vessel, the intima was always intact and at no point were there any traces of rupture. The aorta showed similar changes. Our opinion is that this is a case of primary medial calcification or hyalinization of doubtful etiology.

Surbek<sup>18</sup> reports an autopsy of a newborn infant three days old, in which were found, as a result of an intrauterine diplococcal infection, fresh fibrinous pericarditis, acute splenic tumor and nephritis with chronic foci of inflammation. The mother had a chronic otitis media with an acute exacerbation; her Wassermann reaction was negative, and no spirochetes could be demonstrated in the child's liver. There was an extensive calcification of numerous organs with a predilection for the arteries. These changes found in the arteries may be summarized as a high degree of calcification of the media with formation of granulation and connective tissue in the region of the calcareous focus, chronic inflammatory infiltration in the adventitia and localized compensatory intimal proliferation without intimal degeneration. There were no inflammatory or degenerative changes found in the media which were not associated with calcification. The inflammatory changes in the adventitia went parallel, in extent and intensity, with the calcification in the media, so that it cannot be stated whether they were the result of the medial calcification or the direct result of the infection. Surbek thinks that the first is more reasonable, and that the condition was due primarily to a disturbance of the calcium metabolism which was expressed in the calcification of the arteries and various organs.

The autopsy reported by Jaffé<sup>19</sup> was that of a boy two days old whose mother suffered from severe hydramnios during pregnancy, but nothing else of importance was given in the history. A study of the vessels revealed a necrotic process localized chiefly in the inner half of the media, and affecting chiefly its muscle fibers. The necrosis was associated with calcification. The elastic tissue within the foci was largely destroyed and partly calcified, while the elastic fibers of the surrounding region had lost their wavy appearance and were peculiarly straight. It is the opinion of Jaffé that the process in this case was chiefly a necrosis which had later undergone calcification, and that it is similar to the vascular affections occurring in the course of acute infections as described by Wiesel.<sup>20, 21, 22, 23, 24</sup> There was no involvement of the intima or adventitia in this case.

## CASE REPORT

A newborn white gentile male, delivered by cesarean section, died at the age of three days, following intermittent attacks of cyanosis and apnea, during which oxygen and artificial respiration were employed. The family history as well as the Wassermann reactions of both the mother and the father was negative. There were no previous illnesses of the mother. At examination before death, marked cyanosis and moderate dyspnea with frequent periods of apnea were noted. The left border of the heart dullness was 3.5 cm. to the left of the midsternal line while the right was 3 cm. to the right. The heart rhythm was regular and the rate 140. The Wassermann reaction on the spinal fluid was negative. Teleroentgenogram revealed

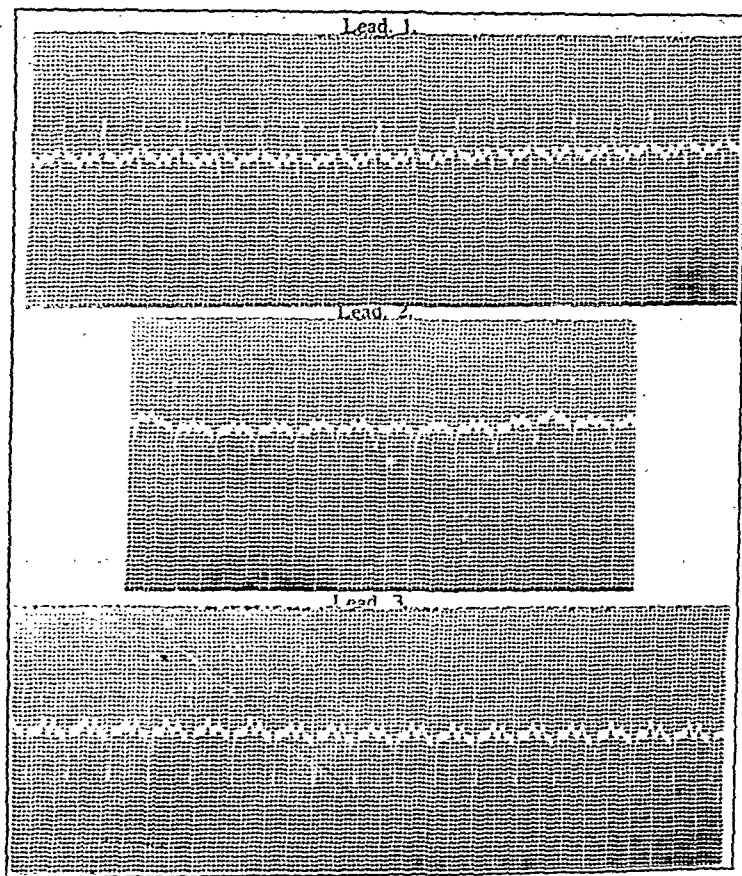


Fig. 1.—The R-T segment Lead I slightly convex followed by pointed inverted T-wave. The P-wave is also inverted, rate 166.

an inside chest diameter of 9.8 cm. with a transverse heart diameter of 6.4 cm. The electrocardiogram (Fig. 1) revealed a regular rhythm, rate 166, with inverted P- and T-waves in Lead I. The R-T interval in Lead I appears to be convex followed by a pointed negative T-wave. At autopsy, eighteen hours after death, the body was found to be that of a well-developed, newborn male child. The body had not been embalmed but was well preserved on ice. There was a moderate amount of livor mortis but no evidence of rigor mortis. There were no malformations or other special marks of identification aside from the usual partially dried stump of the umbilical cord. Upon opening the body, no pathological changes were found in the abdominal cavity. In the thoracic cavity, scattered areas of petechial hemorrhage were found in the parietal pleura. The lungs were partially expanded and showed scattered areas of fresh hemorrhage into the lung parenchyma



Fig. 2.—The right anterior aspect of the heart showing the prominent, whitish and thickened right coronary artery.

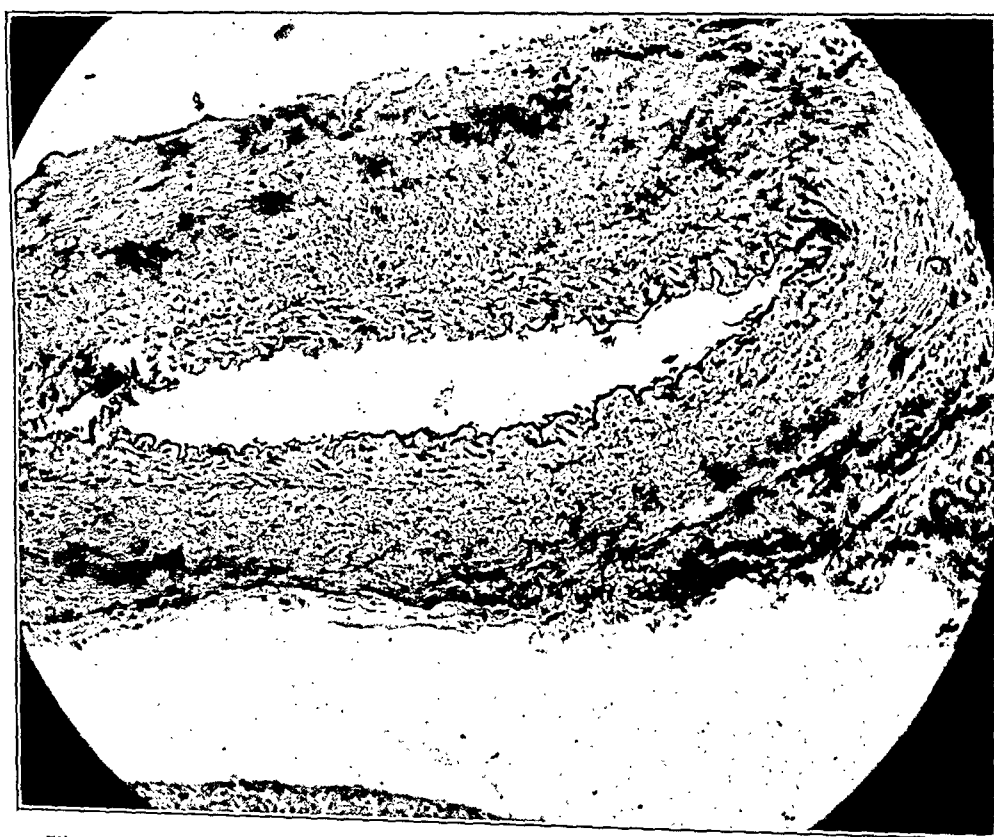


Fig. 3.—Low power view of one of the thickened coronary arteries. Note the normal lumen and tunica intima. The replacement of normal muscle by the connective tissue process in the media is present throughout the entire wall but is especially noticeable in the upper right portion.

and smaller bronchioles. The thymus was normal in size. The pericardial area was enlarged, measuring six and one-half centimeters in transverse diameter. Upon opening the pericardial sac it was found to be smooth, free from petechial hemorrhages and to contain the usual amount of clear fluid. Inspection of the heart *in situ* showed it to be slightly enlarged and to have an unusual degree of coronary prominence. The coronary arteries, especially the right, were opaque, white in color, almost cordlike, quite prominent but not tortuous. Upon palpation they were quite firm and cordlike (Fig. 2). Upon removal and opening the heart no abnormalities were found. The foramen ovale was closed. Cut section of the coronaries revealed no occlusion by thrombi or obliteration by intimal thickening. The intima upon gross examination was quite smooth and free from lipoid deposits or other evidence of thickening. The firmness and thickening appeared to be

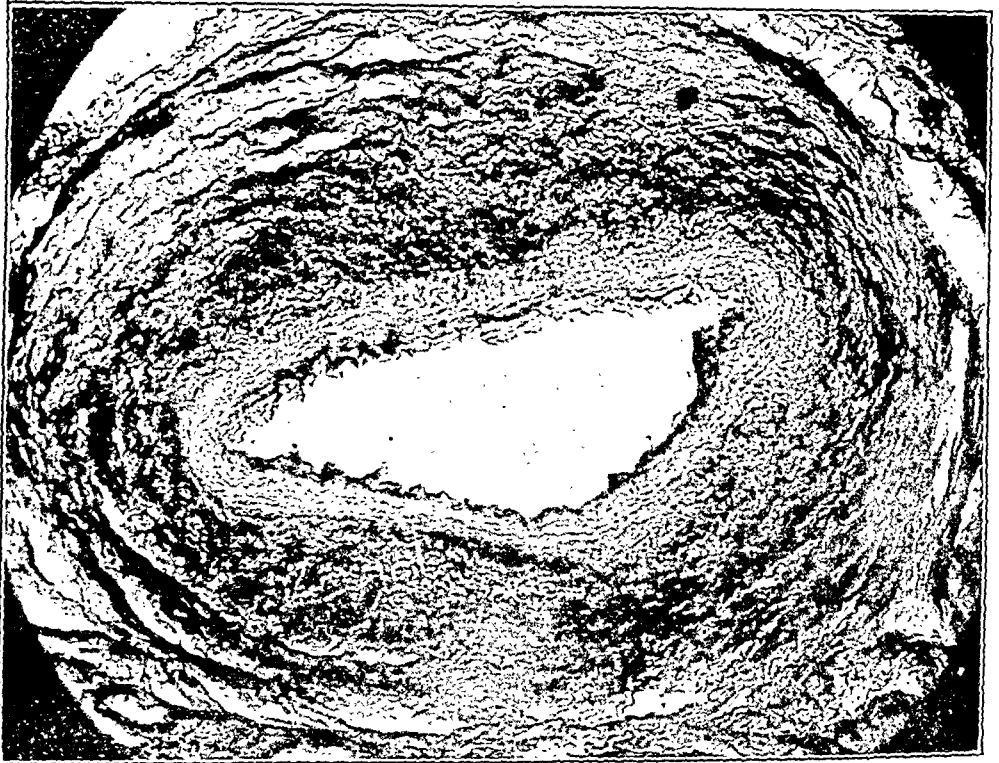


Fig. 4 —Picro-acid-fuchsin stain of the thickened coronary. Note the normal intimal layer, the marked connective tissue formation in the media, and the normal adventitia.

within the medial layer of the arteries. The brain revealed no pathological changes and the cerebral arteries were entirely normal.

Microscopical sections prepared from the thickened coronary arteries and stained with eosin-hematoxylin and picro-acid-fuchsin stains showed definite changes in the medial layer. With the eosin-hematoxylin stains (Fig. 3) the endothelium could readily be identified and subendothelial tissue was lacking, while the inner elastic membrane was present throughout and was folded in the usual manner by the post-mortem contraction of the vessel. The tunica intima was therefore considered normal, showing no thickening or deposits, and the lumen was open and normal. In the medial layer the muscle cells could be easily identified just external to the inner elastic membrane, but passed rather abruptly into a zone of poorly staining, almost hyaline-like degeneration, which zone produced the great thickening noted in the gross specimen. The tunica externa was normal, and in none of the sections could evidence of cellular infiltration or of infection be found. The sec-

tions stained with the picro-acid-fuchsin (Fig. 4) also revealed the intimal layer to be entirely normal, but within the medial layer definite changes were noted. The circular and oblique muscles of the tunica media were present throughout in a thin layer immediately external to the inner elastic membrane, staining a pure yellow. The external portion of this thin muscle layer was invaded to an abnormal extent by red staining connective tissue, which formed a zone corresponding to the poorly stained zone above described external to the muscle. This zone of connective tissue was approximately twice as thick as the muscle layer and was entirely lacking in the sections of normal coronary arteries examined. There was no evidence of calcification within this zone. The tunica externa formed a

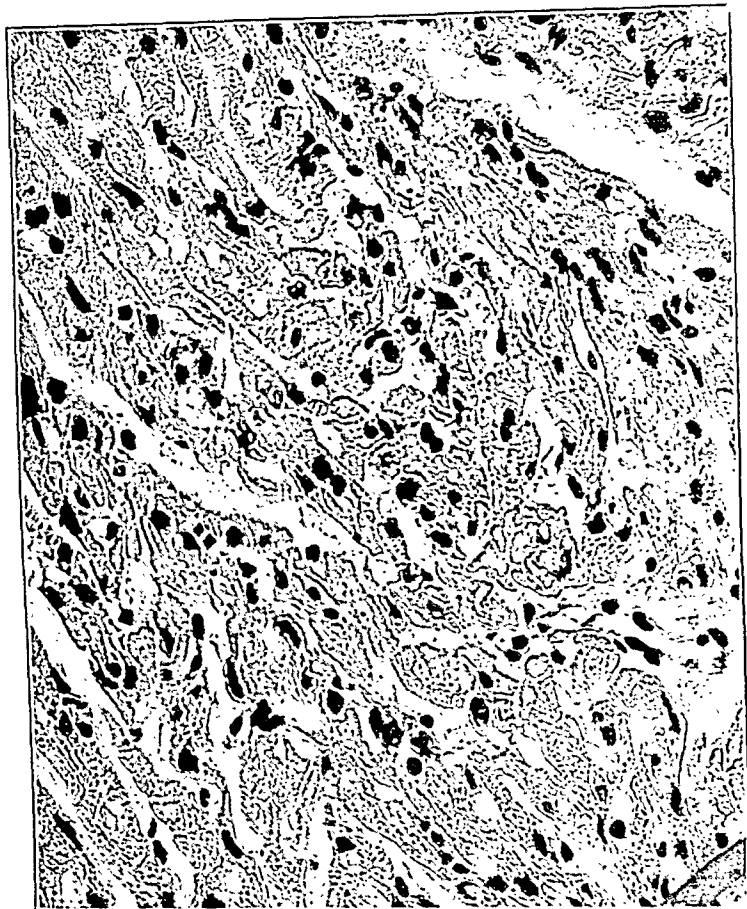


Fig. 5.—Medium power view of a section of heart muscle supplied by the thickened coronary branch. Note the edema of the muscle and loss of normal striations.

definite layer external to this and consisted of the usual number of longitudinal elastic fibers throughout which were the normal number of apparently unchanged longitudinal muscle cells. There was no cellular infiltration or cellular accumulations in the adventitia. Sections examined from the myocardium of both ventricles in the areas supplied by these coronary arteries showed a diffuse edema of the muscle cells with certain areas of hydrops and loss of striation (Fig. 5). The smaller branches of the coronary arteries within the myocardium were free from pathological changes. The diagnosis of congenital noninflammatory medial sclerosis of the coronary arteries was made.

For the purpose of comparative study the normal heart of a newborn infant was obtained at autopsy. The coronary arteries were not found to be prominent, opaque or cordlike, and the walls were thin and could readily be collapsed by the

slightest pressure. Microscopical sections were prepared from these normal arteries and stained with eosin-hematoxylin (Fig. 6) and picro-acid-fuchsin (Fig. 7) stains. The endothelium could readily be identified, and immediately external to this was the folded inner elastic membrane. The subendothelial tissue was lacking, thus making the tunica intima thin and distinct. In the tunica media the muscle cells were abundant, well stained, and formed a thick layer which was only sparsely invaded by elastic and connective tissue cells. The circular and radial elastic fibers were few in number and were not increased toward the tunica externa. The tunica externa consisted of longitudinally arranged connective tissue and elastic fibers, intermixed with an occasional muscle cell, and there was no definite formation of an external elastic membrane.

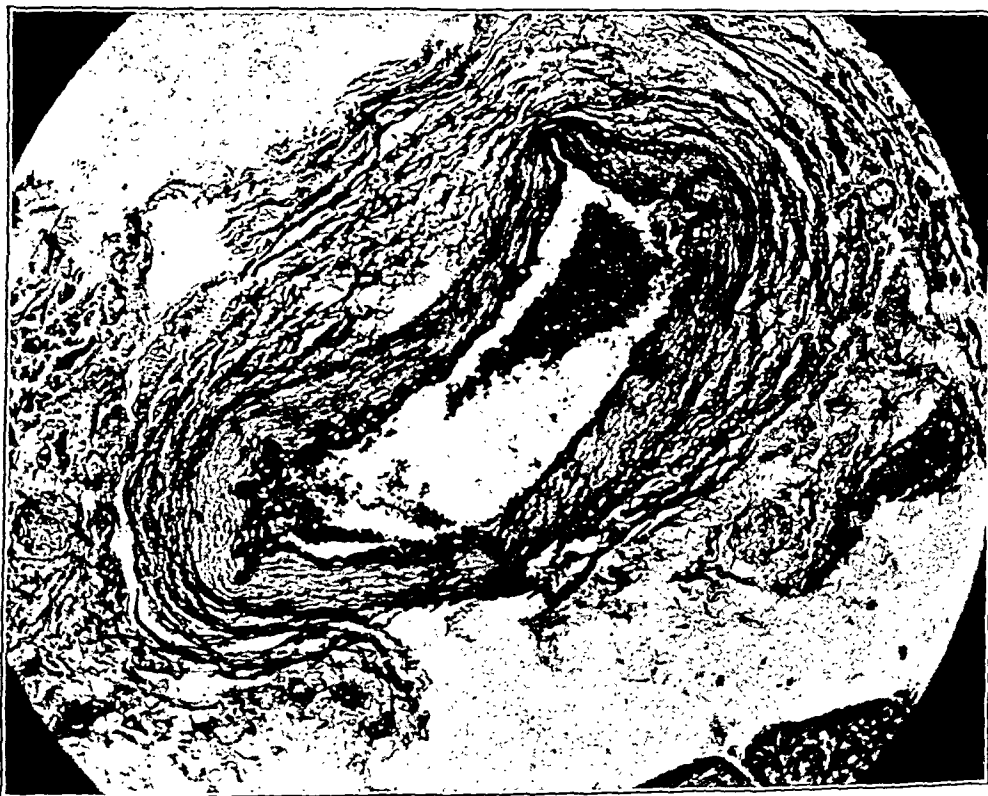


Fig. 6.—Eosin-hematoxylin stain of a normal coronary artery. Note the well-formed muscle cells in the media and the small amount of connective tissue.

#### PATHOLOGICAL DISCUSSION

This discussion is limited to those conditions in which the pathological changes involve the media primarily, disregarding atheromatosis and changes of the intima and adventitia which only involve the media secondarily.<sup>54</sup> The characteristics of these medial changes are connective tissue formations, calcification, fatty infiltrations and toxic and inflammatory degenerations, which are characterized by hyaline and amyloid replacements and which may be followed by calcified scars.

Degenerative changes varying from simple edematous infiltration to marked necrosis with complete disappearance of the elastic fibers have been frequently found following infectious-toxic diseases, such as scar-



let fever, diphtheria, measles, typhoid, influenza, pyemia, eclampsia and endocarditis.<sup>12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24</sup> These conditions lead to circulatory weakness which may be fatal, and are frequently found in the coronary arteries,<sup>20, 21, 22, 23, 24</sup> especially the anterior descending branch of the left coronary.<sup>51</sup> Depending upon the severity of the condition, the media may be restored to normal or may undergo scarring or calcification with the intima and adventitia remaining intact.<sup>20</sup> The cases of Hughes and Perry,<sup>52</sup> Durante,<sup>53</sup> Surbek<sup>18</sup> and Jaffé<sup>19</sup> appear to be of this type with resulting calcification.

These calcium deposits occurring in the medial layer, secondary to degenerative changes, are thought by Kaufmann<sup>54</sup> to be preceded by fatty

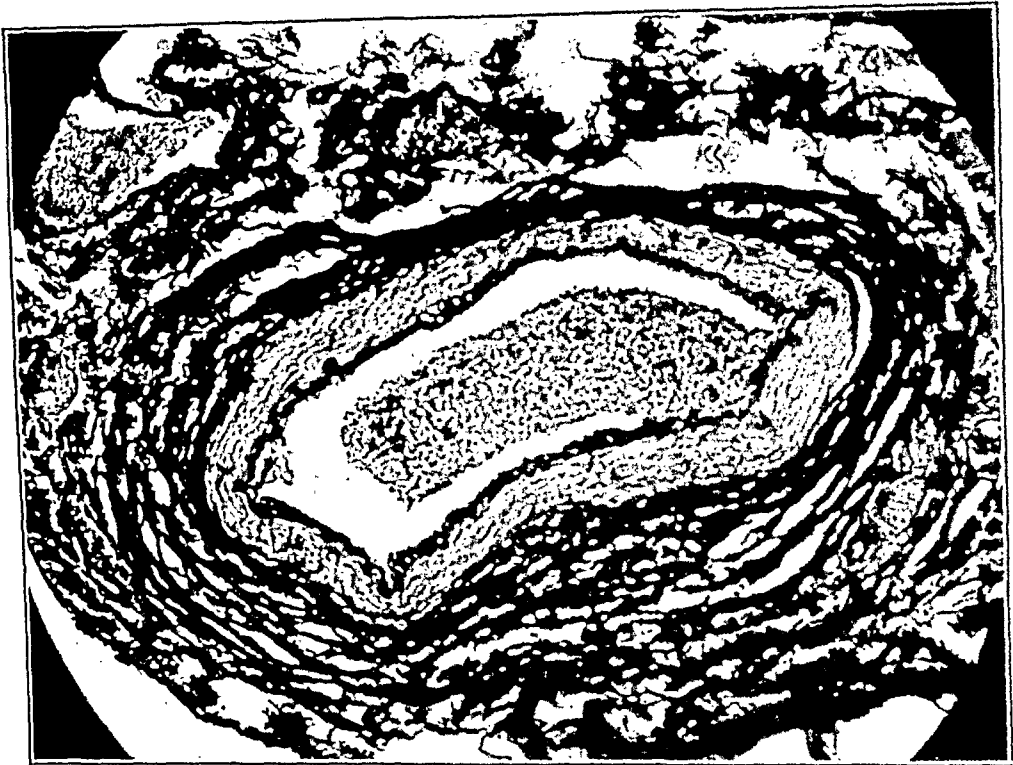


Fig. 7.—Picro-acid-fuchsin stain of a normal coronary. Note the normal thickness of the medial layer and few connective tissue cells.

and hyaline changes, while others consider them to be preceded only by the hyaline changes.<sup>55, 56, 57</sup> Wiedermann<sup>58</sup> believes that the process starts in the adventitial lymph sheaths and involves the media later. The mobilization and deposition of calcium in the media due to hypervitaminosis have been frequently observed,<sup>43, 44, 45, 46, 47, 48, 49, 50</sup> and, following irradiated ergosterol, necrosis of smooth and striated muscle in the rat is reported.<sup>50</sup> Kreitmar and Moll<sup>49</sup> believe that hypervitaminosis produces a mobilization of calcium, in which process calcific deposits develop in necrotic muscle foci, in healthy heart muscle and in otherwise unchanged elastic fiber, and they also demonstrate that the necrosis and calcification produced in arteries by vigantol is in reality true

medial calcification and is sharply differentiated from intimal sclerosis.

Calcification of the primary type always begins in the media between the muscle cells and consists of the laying down of calcium granules with the later replacement of the muscle fibers.<sup>54</sup> The muscle fibers are at first well preserved between the foci of calcium, and it is assumed that they degenerate secondarily.<sup>10</sup> This is true of the medial sclerosis of Mönckeberg in which there is usually no intimal change, although the intima may become stretched over wide calcified areas in the media, and has definitely been differentiated from arteriosclerosis by Mönckeberg<sup>8, 9, 10</sup> and by Fischer.<sup>50</sup> If we exclude hypervitaminosis with mobilization of calcium from the list of possible causes of this type of calcium deposition, we are led to the conclusion of Mallory<sup>55</sup> that the process is one of metaplasia of the fibroblastic elements. Orliansky<sup>16</sup> states that calcification of the medial layer of the coronary arteries is rare, while Mönckeberg<sup>8, 9, 10</sup> found it frequently, especially in the left coronary artery, beginning early in life.

The medial necrosis following infection<sup>20, 21, 22, 23, 24</sup> and reported in the cases of Jaffé<sup>19</sup> and Gsell<sup>60</sup> is described as similar to the changes produced by Josué<sup>34, 60</sup> with the intravenous injection of adrenalin. The lesion is primarily localized in the media in its inner two-thirds and begins with fatty degeneration of the muscle cells and elastic fibers, and it is assumed that the fat arises from the broken down muscle cells and is followed by calcification.<sup>61, 62, 63, 64, 65, 66</sup> The intima and adventitia do not show changes. Dominguez<sup>33</sup> finds that spontaneous medial necrosis can also be produced in rabbits by uranium poisoning and that in such cases adrenalectomy did not prevent the development of the lesion.

Fatty degeneration in the media is common, occurring early in childhood and even in suckling infants.<sup>54</sup> The media of the smaller arteries of the brain, is especially prone to such change. This lesion is described as being the beginning pathological change in the sclerosis of Mönckeberg,<sup>10</sup> necrosis due to adrenalin,<sup>62, 63, 64, 65</sup> intoxication from alcohol and phosphorus, and the calcification from irradiated ergosterol.<sup>68</sup>

Connective tissue formation in the tunica media is usually inflammatory in origin, as in the case of McMichael.<sup>52</sup> The case herein reported falls into this group but is unique in the entire absence of any infectious process, neither did it show fatty degeneration, necrosis, cell infiltration, or calcification. The case of congenital sclerosis reported by Hughes and Perry<sup>53</sup> is described as having a thickened intima and therefore is not considered primary medial sclerosis, while the case presented here showed the intima not to be involved. It is interesting to speculate as to whether this is not an early type of Mönckeberg medial sclerosis of the coronary arteries, in which the change is only one of hyaline and connective tissue, and in which further development of the process would result in calcium deposition within the tunica media.

The clinical findings of paroxysmal cyanosis and apnea with moderate cardiac enlargement and an electrocardiogram showing a slightly convex R-T interval followed by a sharp pointed negative T-wave in Lead I, suggest a possible method of diagnosing this condition before death. The T-wave in Lead I is very similar to the coronary T-wave described by Pardee.<sup>60</sup> This condition is present probably more frequently than a review of the literature would suggest, and all cases of the so-called congenital idiopathic cardiac hypertrophy should be investigated for these pathological findings.

#### CONCLUSIONS

1. A case of congenital medial sclerosis of the coronary arteries is reported with a review of the literature.
2. The process is noninflammatory and is characterized by a primary medial thickening, confined to the larger coronary branches.
3. The process is probably an earlier stage than those previously reported.
4. The electrocardiogram shows a T-wave similar to that seen in the more familiar types of coronary sclerosis.
5. The name of congenital medial sclerosis of the coronary arteries is suggested.

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## RHEUMATIC HEART DISEASE:

### I. INCIDENCE AND RÔLE IN THE CAUSATION OF DEATH. A STUDY OF 5,215 CONSECUTIVE NECROPSIES\*

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THE incidence of heart disease may be determined by examining a large series of unselected post-mortem records and correlating this data with that concerning the clinical course of the illness. Such a combined morphological and clinical study is particularly essential to an accurate estimation of the incidence and importance of rheumatic heart disease, for statistics based on clinical studies alone may fail to include a considerable number of cases. Without a correlation of both clinical and morphological findings it would be difficult also to determine the degree of the cardiac damage caused by rheumatic fever. Furthermore it would be difficult to differentiate the various types of acute valvulitis, such as rheumatic, subacute bacterial, or malignant endocarditis. Thus, in the present study of the incidence of death from rheumatic heart disease it would have been impossible to classify approximately 30 per cent of the cases from the autopsy records alone.

It is conceivable that rheumatic fever may cause cardiac damage of such slight degree as to be unrecognizable on morphological examination. If cases of this type do occur they would obviously not be revealed by the present analysis.

#### METHOD OF INVESTIGATION

The material on which the present study was based consisted of 5,215 consecutive necropsy records from the Department of Pathology of the Boston City Hospital, covering a period from 1905 to 1929 inclusive, and compiled under the direction of Dr. Frank B. Mallory. These records represented gross and histological studies by various members of the staff. Each autopsy record had been reviewed by Doctor Mallory and the junior pathologists. Rheumatic and allied lesions were described without any attempt to classify or interpret their etiology. The term "vegetative endocarditis" appeared frequently in the final anatomical diagnosis; the term "rheumatic" was seldom used. The problem of etiology, therefore, was not influenced by the morphological diagnosis but was determined from the combined available data.

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No microorganism or immunological reaction has been found to be characteristic of rheumatic fever or of rheumatic heart disease; and as the clinical course and structural changes in the heart vary considerably, the diagnosis may present difficulties even when all available data have been studied. This is particularly true in the milder forms, which, as is true in other infectious diseases, may well occur more frequently than is suspected.

The few studies in the literature which report the incidence of rheumatic heart disease give no description of the method used in the selection of cases. It is possible that several important considerations were neglected in these studies. We had so much difficulty in distinguishing the rheumatic cases from cardiac diseases of other etiology, that a summary of the procedures followed in this selection seems essential.

The autopsy records were examined for such evidence of rheumatic heart disease as cardiac enlargement, acute or chronic pericarditis, myocarditis with Aschoff-like lesions on microscopical examination, acute valvulitis, chronic valvular sclerosis and associated sclerosis and shortening of the chordae tendineae and papillary muscles. Records showing sufficient evidence of rheumatic etiology were then correlated with the corresponding clinical data. The clinical aspects emphasized were: the age of the patient; a history of rheumatic manifestations, such as characteristic arthritis, chorea, and repeated attacks of severe tonsillitis and fever; the duration and character of the illness; and any clinical evidence of the existence of cardiac lesions or circulatory failure. The final selection was based upon a combination of these factors. Obviously such an analysis did not guarantee an absolutely accurate selection in each case. Rigid classification, however, in a disease of such wide variation would be unjustified.

#### THE PROBLEM OF DIFFERENTIAL DIAGNOSIS

A majority of the cases studied showed unmistakable evidence of rheumatic heart disease and were classified accordingly. It was difficult, however, to identify and evaluate that group in which the rheumatic heart disease, if present, was slight and the cardiac condition only a partial factor in causing death. It was necessary to differentiate these chronic stages of rheumatic endocarditis from atheromatous, luetic, and other types of sclerosis of the valves, and from endocarditis of other etiology. Examination of cases with uncomplicated primary atheromatous valvular heart disease revealed that the process involved only in rare instances cusps of the mitral as well as of the aortic valves, causing sclerosis and stenosis at the same time; and that senescent degeneration did not produce thickening and shortening of the chordae tendineae and papillary muscles similar to that in rheumatic heart disease. *Primary calcification of the valves* was uncommon; it occurred

generally in advanced age, and was usually associated with atheromatous lesions in the aorta. When the calcification involved the mitral valve, it was generally confined to the aortic mitral cusp and the gross character of this process, the usual fatty changes and frequently a calcified ring along the base of the mitral valve made it readily recognizable in most cases. The healed lesions in cases unmistakably of rheumatic etiology, on the other hand, occurred in practically every instance along the free margins, at the line of contact, causing thickening at the edges. These lesions contrasted strikingly with those of *syphilitic endocarditis* in which there is almost always widening of the commissures usually associated with luetic lesions in the aorta. Occasionally there was evidence that both etiological factors were present and such cases were listed accordingly.

In the course of the investigation several patients with acute vegetative lesions were examined; and it was again essential to determine which of these were truly rheumatic. Acute *bacterial endocarditis* secondary to a septic focus elsewhere in the body was recognized and excluded without difficulty: the presence of the primary infection, the friable irregular vegetations generally containing large numbers of bacteria, the suppurative processes and local evidence of destruction of the valves were sufficient to make the diagnosis definite. Effort was made to determine when such an acute vegetative process was superimposed on an old rheumatic process and such cases were listed separately. All cases showing a primary acute bacterial endocarditis were listed to determine the frequency of their occurrence in relation to old rheumatic lesions. The so-called *marantic* or *toxic acute endocardial* lesions occasionally seen in patients dying of tuberculosis, malignant tumors, and chronic nephritis were not a source of error. These lesions at most would have been included in the group of noncontributing rheumatic heart disease and in this group we noted only one case of acute rheumatic heart disease without the unmistakable old endocarditis accompanying it.

A few pathological descriptions mentioned delicate *adhesions between the valves of the aortic cusps*. Such adhesions were not regarded as indicative of a rheumatic process, for they occurred with fair frequency in patients with atheromatous involvement of the same valve. A rheumatic history was not obtained in these cases. In a few other instances hearts were observed with one or two *single vegetations* varying from one to five millimeters in diameter and occurring generally on the mitral or aortic and very rarely on the tricuspid or pulmonary valves. These cases also were excluded from the series for lack of other evidence as to their etiology.

In a number of cases details of the gross description of the acute vegetative process, post-mortem heart blood culture, and microscopical examination of the valve, were lacking. Similarly the clinical



description occasionally did not contain the data needed to interpret the individual case. Three per cent of the cases taken under consideration were excluded because of such inadequacy. After a careful examination of the data in respect to the criteria indicated above, the cases with rheumatic heart lesions were classified into the groups listed in Table I.

TABLE I  
DISTRIBUTION OF RHEUMATIC HEART DISEASE AMONG 5215 NECROPSIES

|  | NUMBER CASES |
|--|--------------|
| I. Rheumatic heart disease directly responsible for death                    | 164          |
| II. Rheumatic heart disease a contributing factor to death                   | 41           |
| III. Rheumatic heart disease associated with subacute bacterial endocarditis | 35           |
| Rheumatic heart disease with doubtful subacute bacterial endocarditis        | 6            |
| IV. Rheumatic heart disease with superimposed primary malignant endocarditis | 16           |
| Rheumatic heart disease with subacute or malignant endocarditis              | 5            |
| V. Rheumatic heart disease with secondary malignant endocarditis             | 2            |
| VI. Rheumatic heart disease a noncontributing factor to death                | 205          |
| Total  | 474          |

*I. Rheumatic Heart Diseases Directly Responsible for Deaths.*—This group includes patients in whom rheumatic heart disease or an immediate complication, such as mural thrombosis with embolism, was the cause of death. Patients in whom infections, such as pneumonia and erysipelas, occurred in the course of progressive and advanced heart failure were also regarded as rheumatic deaths.

The factors used in the classification of the cases in this group have been described above. A large percentage of the patients gave evidence of an active carditis with an acute vegetative process involving both mitral and aortic valves. These vegetations caused by rheumatic fever consisted of a series of closely aligned, pearly-gray, rounded bodies varying in diameter from 0.5 to 2.0 mm. and occurring regularly along the free margin of the valves. In the majority of instances the diameter was noted as 1 mm. or less. The aortic and mitral cusps, less commonly the tricuspid and rarely the pulmonary cusps were involved. At times the vegetations were described as slightly roughened and irregular in contour. They were generally adherent to the valve leaflet and could be detached only with great difficulty. In very acute lesions the vegetation was occasionally coated with fibrin, as indicated by microscopical examination, and when this accumulated, it occasionally resembled a friable vegetation, such as is seen in bacterial endocarditis. The rheumatic acute vegetations were free of bacteria except for a few instances in which there was question of bacterial complication. Ulceration in an old chronic rheumatic proc-

ess was extremely rare and when present suggested a healed process of an old malignant or subacute bacterial endocarditis.

Four of the patients listed in this group showed primarily a myocarditis with little or no evidence of an endocarditis. Idiopathic myocarditis might be considered but would be ruled out by the fact that in three of these patients there was a definite history of arthritis and fever, probably rheumatic; in one, a suggestive history recorded as "rheumatism."

*II. Rheumatic Heart Disease a Contributing Factor to Death.*—Patients dying of heart failure with pronounced rheumatic lesions were regarded as "rheumatic contributing" when the cardiac pathology was also the result of other etiological factors. The presence of arterial hypertension of long standing, coronary disease, or an associated severe anemia required this special grouping. In several of these patients death occurred beyond the age of sixty when such a factor as arteriosclerotic heart disease demanded consideration in the interpretation of the death.

*III. Rheumatic and Subacute Bacterial Endocarditis.*—In the entire series of 5,215 autopsies there were 47 cases of subacute bacterial endocarditis with and without evidence of an old rheumatic endocarditis. Of the 47 cases, 35 gave evidence of a previous rheumatic infection in the form of a definite old rheumatic endocarditis discovered by gross examination or from a characteristic clinical course. The records represent routine studies only, and although these were often elaborate and detailed in the presence of an atypical vegetative process, it is likely that the primary rheumatic basis in some of the remaining cases escaped detection. This is to be expected, for it is known that even slight valvular damage may serve as a basis for superimposed infection. Furthermore, the destruction occurring in subacute bacterial endocarditis is often sufficient to obscure underlying primary valvular damage. Again, in the group under consideration there was occasionally an unmistakable history of repeated attacks of rheumatic fever without evidence of a chronic rheumatic heart disease underlying the subacute bacterial process.

The vegetative process usually consisted of one or more conglomerated irregular masses varying from 2 mm. to 1 cm. in diameter, and distributed over the mitral, aortic, and, rarely, the tricuspid valves. The left auricular endocardium was frequently involved in a widespread process which extended over the mitral cusps, chordae tendineae, and papillary muscles, causing ulceration and destruction. These masses of vegetations were regularly friable, and microscopical examination generally revealed large numbers of streptococci. In the early stage the vegetations were often small and at times discrete. The irregular friable character, the positive microscopical findings, and the clinical observations made the diagnosis definite in most cases.

In contrast to the rheumatic group with an active carditis, secondary anemia was regularly present in cases with subacute bacterial endocarditis. The frequent occurrence of embolic phenomena secondary to mural thrombi and possibly fibrinous rheumatic vegetations in cases of rheumatic heart disease interfered with the application of "embolic phenomena" as differential criterion between subacute bacterial and rheumatic endocarditis.

Bacterial processes showing *Streptococcus viridans* either in ante-mortem blood culture or early post-mortem vegetation culture, or histological sections were generally classified in this group. In a few cases it appeared that a *Streptococcus viridans* infection with a subacute bacterial course gave evidence of terminal infections with a pneumococcus or staphylococcus. Cases of this kind were classified in the subacute bacterial group. Vegetations yielding *Staphylococcus aureus* as the predominant organism were classified in the group of malignant endocarditis. The latter group, although not sharply defined, presented a more acute clinical picture with a shorter duration of the illness, a more fulminating termination, a greater tendency to local destruction and perforation of the valves and to septic emboli.

In one group of cases it was difficult to decide whether an acute process associated with an old rheumatic endocarditis belonged to the rheumatic manifestations or represented a secondary bacterial endocarditis, possibly of *Streptococcus viridans* origin. In 6 cases no decision could be reached because of insufficient data or the atypical character of the lesions. In all 6 cases, however, there was undoubted evidence, clinical and morphological, of an old rheumatic process.

*IV. Rheumatic Heart Disease With Primary Malignant Endocarditis.*—Cases in this group were often not clearly distinguishable from those in Group III. In general, patients showing an acute or subacute bacterial infection that developed on the basis of old valvular damage and was caused by *Staphylococcus aureus*, *Streptococcus hemolyticus*, pneumococcus, gonococcus or meningococcus, and not by *Streptococcus viridans*, were classified in this group. Other sources of the bacteremia than the vegetations were not found in these cases. Further indications in the classification were the more fulminating acute illness of septic character, and the tendency to marked local destruction and the formation of septic emboli as noted above. Although ulceration and destruction of the valve occasionally occurred in subacute bacterial endocarditis of *Streptococcus viridans* origin, it was almost a constant finding in the malignant group. Undoubtedly, some cases listed in this group might more properly have been listed in Group III and *vice versa*.

Although an effort was made to find cases of this type which occurred primarily on a normal valve, none was evident. In all 14 cases

of the group unmistakable evidence of either a previous rheumatic endocarditis or a clinical history of early rheumatic fever was present.

*V. Rheumatic Heart Disease With Secondary Malignant Endocarditis.*—Two patients with a primary septic focus in the lungs and kidneys respectively showed an old rheumatic lesion associated with a superimposed acute bacterial endocarditis. In a picture of this complexity it was difficult to determine to what extent the cardiac lesions contributed to death. The patient might have died from the pneumonic process or the pyelonephrosis regardless of the endocarditis, or possibly from a primary acute malignant endocarditis, the distal process being really secondary to it. The pathogenesis not being clear from the history and clinical findings, these cases were listed as a secondary invasion of the valves, from the focus elsewhere in the body.

*VI. Noncontributing Rheumatic Heart Disease.*—In this group were listed those cases in which death was not due to the rheumatic pathology. The criteria by which the mild rheumatic process was detected were often not absolutely definite. In the 205 cases listed in this group the valvular process was graded as moderate or marked in 100. These cases were definitely rheumatic. The remaining 105 showed slight but definite mitral and aortic endocarditis. In all cases the process was located along the free margin of the valves. Slight thickening of the free margins of the valves is a common post-mortem finding, particularly after the fifth decade of life, and may be an expression of senescent sclerosis. The thickening regarded here as probably of rheumatic origin should not be confused with this for the following reasons: the sclerotic changes are much more common than the mere 5 per cent of the cases noted; the age variation in this group with slight involvement indicated a wide distribution with numerous cases below the age of forty; and the examiners did not list all cases with thickening of the free margins as cases of endocarditis, but did record and list as "endocarditis" over 95 per cent of the 105 cases considered here as probably rheumatic. Furthermore, the cases were evenly distributed over the entire twenty-five year period of analysis, suggesting that the examiners recognized these cases as different from those of the usual valvular thickening. Finally, the distribution to both mitral and aortic cusps paralleled that of the cases with advanced rheumatic endocarditis. The occurrence of mild grades of any disease is to be expected and for the above reasons it appears that these cases probably represent valvular pathology due to a mild rheumatic infection and something more than the diffuse increase in thickness of the free valvular margins seen so commonly in routine post-mortem examinations.

#### DISCUSSION

Exact information concerning the incidence and relative significance of the various types of heart disease is important, particularly from

the point of view of public health. The efficacy of preventive and therapeutic measures commonly used in heart disease can be evaluated only by a study of reliable statistical data. Such information, moreover, may throw light on such etiological factors as race, geographic location, and climate.

Numerous statistical sources may give significant information regarding the incidence of heart disease, but at present the value of available reports is impaired by the unreliability of the original data. Statistics on the morbidity rate, for example, are based on clinical evidence alone and are therefore as subject to inaccuracy as the diagnosis on which they are based. The figures on mortality rate derived from death certificates are notoriously unreliable. The statistics, even of hospitals, are often of doubtful value because of confusion in the classifications of diseases and insufficient effort in differentiating between primary and contributory causes of death.

Practically no information is available concerning the incidence of rheumatic heart disease. The criteria of diagnosis and the methods of accumulating data on this subject vary widely. Cohn,<sup>1</sup> after reviewing the literature regarding factors which influence rheumatic heart disease, concludes: "The data inspire no great confidence and suggest that the conditions under which they are correlated should be more precisely defined."

Harrison and Levine<sup>2</sup> report the occurrence of mitral stenosis 64 times in 1,362 consecutive necropsies at the Peter Bent Brigham Hospital, an incidence of 4.69 per cent. Of 15,932 medical admissions to this same institution between the years 1914 and 1923, 3.89 per cent gave clinical evidence of mitral stenosis. These data obviously cannot be regarded as an indication of the incidence of rheumatic heart disease and occasionally such stenosis is due to atheromatous sclerosis. This is illustrated by our finding of only 66 cases of mitral stenosis among the total 164 cases with marked rheumatic heart disease. If we had judged the frequency of rheumatic heart disease by the cases of mitral stenosis alone, we would have obtained a frequency of only 4.0 per cent, comparable to the figure of Harrison and Levine, instead of 9.1 per cent. Cabot<sup>3</sup> analyzed 4,000 necropsy findings in the Massachusetts General Hospital for the period from 1896 to 1919. He reported 208 cases of "rheumatic valvular heart disease" but apparently did not classify all the types of cardiac damage produced by rheumatic fever.

Of the 5,215 necropsy records in the present investigation, 486 cases of cardiac pathology were classified as of rheumatic origin, an incidence of 9.3 per cent. If we subtract from the rheumatic series the cases with subacute endocarditis in which evidence of rheumatic etiology could not be established, the incidence is 9.1 per cent. If the 105 cases with slight cardiac lesions are not included in the total group

of rheumatic heart disease, the incidence of the remaining cases is 7.1 per cent. This incidence of 9.3 or 7.1 per cent respectively is distinctly higher than had been expected from the few available reports in the literature. There may be a number of explanations for this difference. The high incidence, in the first place, is reported from a locality where rheumatic fever is probably conspicuously prevalent.<sup>2, 4</sup> Furthermore, these observations are from a municipal hospital which cares mainly for patients of limited means, drawn for the most part from the crowded sections of a large city. Insufficient nutrition and light, the influence of which on rheumatic heart disease is important may partially account for the relatively frequent occurrence of the condition in the present series. The most important factor in the explanation of the high incidence noted, however, is that in previous reports only the obvious and marked lesions were recognized. In the present study, on the other hand, equal attention was given to the less pronounced but nevertheless distinct endocardial and myocardial lesions. These milder cardiac lesions, probably, were the outcome either of a mild rheumatic fever or of a more severe attack from which recovery was more complete. These mild lesions, as a rule, produced few or no clinical signs. The frequent occurrence of slight rheumatic cardiac lesions may be compared with the common "forme fruste" manifestations of other infectious diseases, such as pulmonary tuberculosis. Leary reports the occurrence of rheumatic endocarditis without systemic manifestations as a frequent accidental finding in a number of medico-legal autopsies.<sup>5</sup> This observation also shows that rheumatic heart disease not infrequently runs a symptomless course. The occurrence of mitral stenosis in approximately 4 or 5 per cent of the total number of admissions to the larger Boston hospitals<sup>2</sup> is, then, in proportion to the 9.3 per cent frequency of rheumatic cardiac damage reported here, for obviously the latter figure, which includes cases without clinical signs, must be considerably higher. Furthermore, Pribram<sup>6</sup> states that from 2 to 5.5 per cent of all admissions to the German and Scandinavian hospitals are rheumatic cases, and in England the frequency of rheumatic fever reaches as high a level as 7 to 11.5 per cent of all admissions. The high incidence of rheumatic heart disease reported here would make rheumatic fever a rather prevalent disease comparable to carcinoma; as the frequency of carcinoma among 3,004 autopsies in the Boston City Hospital between 1910 and 1928 inclusive, was 10.4 per cent.<sup>7</sup>

Rheumatic heart disease occurred in 56.6 per cent of the males in the total group with rheumatic heart disease; in 43.4 per cent of the females in that group. This indicates a moderately increased incidence of rheumatic heart disease in the female sex, since the sex ratio in 5,060 autopsies during the same period of years was 62 per cent

TABLE II

DISTRIBUTION OF RHEUMATIC HEART DISEASE ACCORDING TO SEX AND COLOR

|   | MALE | FEMALE | COLOR |
|---|------|--------|-------|
| I. Rheumatic heart disease directly responsible for death                     | 82   | 82     | 10    |
| II. Rheumatic heart disease a contributing factor to death                    | 26   | 15     | 1     |
| III. Rheumatic heart disease associated with sub-acute bacterial endocarditis | 33   | 13     | 4     |
| Rheumatic heart disease with doubtful sub-acute bacterial endocarditis        | 5    | 1      | 0     |
| IV. Rheumatic heart disease with superimposed primary malignant endocarditis  | 13   | 3      | 2     |
| Rheumatic heart disease with subacute or malignant endocarditis               | 1    | 4      | 0     |
| V. Rheumatic heart disease with secondary malignant endocarditis              | 110  | 95     | 1     |
| VI. Rheumatic heart disease a noncontributing factor to death                 | 2    | 0      | 0     |

male to 38 per cent female. This finding accords with the clinical impression that the disease occurs somewhat more frequently in females.

Eighteen, or 3.8 per cent, of the 474 patients with rheumatic heart disease were negroes; but since 8 per cent of the 5,060 consecutive autopsied cases were in negroes, the actual incidence of rheumatic heart disease in this racial group is relatively lower. Whether this difference is inherent in the race, or is due to migration after childhood from a warmer climate where rheumatic fever is a rare disease<sup>2, 4</sup> cannot be stated. Clinical impression suggests that native negroes and northern whites are equally susceptible to rheumatic fever. The lower incidence would thus appear to be due to migration. The finding of rheumatic heart disease in 3.8 per cent of the post-mortem examinations of negroes probably, therefore, represents an average of these two different sections of the negro population.

## SUMMARY AND CONCLUSIONS

1. Among the 5,215 consecutive necropsy examinations of patients from the poorer class who were cared for in the Boston City Hospital between the years 1905 and 1929 inclusive, a combined clinical and morphological study revealed rheumatic heart disease in 474, or 9.1 per cent, of the cases.

2. Rheumatic heart disease was found in 56.6 per cent of the males, and in 43.4 per cent of the females in the group with rheumatic heart disease. The sex distribution in the total necropsy examinations was: males, 62 per cent; females, 38 per cent. Thus rheumatic heart disease was slightly more prevalent among the females.

3. Eighteen, or 3.8 per cent, of the total number with rheumatic heart disease were negroes. Eight per cent of the autopsied patients were negroes. This would indicate that rheumatic heart disease oc-

curs only about half as frequently among negroes living in New England as among the white race.

4. Rheumatic heart disease was directly responsible for death in 164 instances, or 34.5 per cent of the total group with rheumatic heart disease.

In an additional group of 41 cases, corresponding to 8.6 per cent of all the cases in this group, subacute bacterial endocarditis was superimposed on rheumatic heart disease. In 21 cases, corresponding to 4.4 per cent of these cases, malignant endocarditis developed in association with rheumatic heart disease. In 2 additional cases, secondary malignant endocarditis was independent of the rheumatic heart disease. As the subacute and primary acute endocarditis developed on previously damaged rheumatic valves, in this group, representing 13 per cent of all cases with rheumatic heart disease, death was caused indirectly by rheumatic heart disease.

Rheumatic heart disease contributed to death in 41 instances, or 8.6 per cent, of the total cases.

In 205 cases, or 43.2 per cent of the cases with rheumatic heart disease, the character of the cardiac involvement was such that the lesions did not contribute to death.

5. Rheumatic heart disease is surprisingly prevalent among the poorer section of the population of Boston. Its frequency (9.1 per cent) approaches that of carcinoma (10.4 per cent).

6. Rheumatic heart disease frequently exists as a mild "forme fruste" manifestation, without causing obvious impairment of the circulation.

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## STUDIES IN CONGESTIVE HEART FAILURE

### XVI. THE CLINICAL VALUE OF THE VENTILATION TEST IN THE ESTIMATION OF CARDIAC FUNCTION\*

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IN THE tenth paper<sup>1</sup> of this series a method of estimating cardiac function was described. This depended on the fact that upon the performance of exercise the degree of dyspnea produced is directly proportional to the ventilation and inversely proportional to the vital capacity. It was shown that variations in the nutritional state of the subjects had a marked effect on the results obtained and hence in order to compare obese persons with thin ones a correction factor for body weight was introduced. The value so arrived at was called the "ventilation index." In this study are reported the results of applying this test to 21 normal persons and to 79 patients.

The test as originally described consisted of performing exercises of four different degrees. As the severest of these (Exercise IV of the former paper) is rather too strenuous for most patients, it has been omitted in this study. Furthermore, whenever a subject had severe dyspnea on the performance of any degree of exercise, the exercises of severer degrees were omitted.

The patients had a careful history and physical examination. Tele-roentgenograms and electrocardiograms were made in the majority of cases, and in a number of instances blood studies were made and basal metabolic rates were determined. Since it was shown in the previous study<sup>1</sup> that patients with hyperthyroidism, with severe anemia, and with chronic pulmonary fibrosis from any cause, usually had high values (i.e., values similar to those found in persons with cardiac disease) on performance of the test, all persons with these disorders were excluded from the present series.

The subjects were classified into groups as follows:

I. Normal: i.e., no symptoms referable to the heart and no evidence of cardiac disease: 21 cases.

II. Cardiac Neurosis: 16 cases.

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### III. Organic Cardiac Disease:

- A. Asymptomatic: 10 cases;
- B. Symptoms on exertion only: 21 cases.
- C. Mild symptoms at rest: 16 cases.
- D. Severe symptoms at rest: 16 cases.

The classification was based entirely on the data other than those obtained from the ventilation test.

The majority of the patients were followed clinically for periods of a year or more after the ventilation test had been made. The clinical data were then compared with those obtained from the ventilation studies and by this means an attempt has been made to evaluate the clinical significance of the method.

The limits of the normal are not sharp for any laboratory test. It was shown in a previous paper<sup>1</sup> that the ventilation index varied within rather wide limits in normal subjects. It was found, however, that the majority of normal subjects had ventilation indices below the levels of 20, 25, and 30 for the three exercises, respectively, and that no normal subject had a curve above each of these points. For this reason we have, in the present paper, classified the values as follows:

1. "Normal" curves; when all points were below the 20-25-30 curve.
2. "High" curves; when all points were above this curve, and
3. "Doubtful" curves when one or more points were above and one or more points were below the 20-25-30 curve.

### RESULTS

A summary of the data is shown in Table I. The findings may be conveniently considered from several different points of view.

*A. The Value of the Ventilation Test in Diagnosis; i.e., in Determining Whether a Patient Has or Has Not Organic Heart Disease.*—As can be seen from Table II, 2 of the 21 normal subjects in the present series had "doubtful" curves; the remaining 19 persons having "normal" values. Of the 16 patients with cardiac neurosis, none had "high" curves, 4 had "doubtful," i.e., borderline curves, and 12 had normal curves. Seven of 10 patients with asymptomatic organic cardiac disease had "normal" curves, 2 were "high" and 1 was "doubtful." Of 21 patients who had organic cardiac disease and symptoms only on exertion, the ventilation test was "normal" in 2; "doubtful" in 4 and "high" in 15. One patient with symptoms at rest had a "doubtful" curve; the other 31 such subjects were "high." No person with symptoms at rest had a "normal" curve.

From these data it seems clear that the ventilation test is of little or no value as a purely diagnostic measure. It is true that as a general rule patients with normal hearts and with cardiac neurosis have normal values, but so do patients with asymptomatic organic cardiac

TABLE I  
VALUES FOR THE VENTILATION INDEX IN NORMAL SUBJECTS, PATIENTS WITH CARDIAC NEUROSIS, AND PERSONS WITH ORGANIC CARDIAC DISEASE  
IN VARIOUS STAGES

[illegible]

disease. Furthermore, one may occasionally encounter a "doubtful" or borderline test in a patient with advanced cardiac disease, as well as in normal subjects and in persons with cardiac neurosis. In about 80 per cent of the cases one can make the correct diagnosis as to the presence or absence of organic heart disease from the ventilation test alone, but this use of the test becomes unimportant when one remembers that by history and physical examination alone a correct opinion can be arrived at in about 90 per cent.

TABLE II

A SUMMARY OF THE VALUES FOR VENTILATION INDEX IN RELATION TO THE CLINICAL STATE

| GROUP                                 |                           | NORMAL          | DOUBTFUL        | HIGH            |
|---------------------------------------|---------------------------|-----------------|-----------------|-----------------|
|                                       |                           | NUMBER OF CASES | NUMBER OF CASES | NUMBER OF CASES |
| Normal subjects                       |                           | 19              | 2               | 0               |
| Patients with cardiac neurosis        |                           | 12              | 4               | 0               |
| Patients with organic cardiac disease | Asymptomatic              | 7               | 1               | 2               |
|                                       | Symptoms on exertion only | 2               | 4               | 15              |
|                                       | Mild symptoms at rest     | 0               | 1               | 15              |
|                                       | Severe symptoms at rest   | 0               | 0               | 16              |

B. *The Value of the Ventilation Test in Prognosis.*—It was shown in the previous paper that in a given patient progression or retrogression of congestive failure could be followed accurately and expressed quantitatively by means of the ventilation test. Changes in the ventilation index are therefore of value in prognosis. The next question

TABLE III

THE VENTILATION INDEX IN RELATION TO PROGNOSIS IN PATIENTS WITH CARDIAC DISEASE

| CHANGE IN CLINICAL STATE IN 12 TO 18 MONTHS               | PATIENTS WITH NORMAL VALUES (20 OR LESS)* | PATIENTS WITH MODERATE INCREASE (20 TO 40)* | PATIENTS WITH MARKED INCREASE (40 OR MORE)* |
|---|---|---|---|
| No progression:<br>Cardiac symptoms unchanged or improved | 9   | 16  | 4   |
| Progression:<br>Cardiac symptoms more severe              | 0   | 6   | 2   |
| Dead  | 0   | 2   | 7   |
| Total cases   | 9   | 24  | 13  |

\*The patients are tabulated according to their ventilation indices for the mildest exercise. They have been followed for from twelve to eighteen months since the observations concerning the ventilation index were made.

is: Can one make a fairly accurate prognosis in regard to a given patient from the results of a single test? Data bearing on this point are shown in Table III, in which the follow-up records for 46 of the subjects are summarized. (All persons were followed for at least a year and some for more than a year after the test.) It can be seen that, in general, the deaths occurred in the subjects who had high values for the ventilation index, and that those with the lowest values usually remained relatively free of symptoms of congestive failure.

However, in the intermediate group, i.e., those with only moderately increased ventilation indices, 2 patients died, 6 were worse, and 16 improved. Even in the group with very high values, 4 patients are better now than they were a year ago.

C. *The Value of the Ventilation Test in Neurotic Patients With Organic Cardiac Disease.*—The facts previously mentioned seemed to indicate that the ventilation test does not supply, in the majority of patients, helpful information in addition to that which can be acquired by the more usual methods. However, in a certain group of cases it seemed to us to yield knowledge which is of aid both in prognosis and in treatment. We refer to those patients who in addition to having definite clinical evidence of organic cardiac disease are also nervous, hypersensitive, and have symptoms of functional origin referable to the heart. This combination of organic heart disease plus cardiac neurosis may occur in men but is seen most frequently in young females with rheumatic heart disease and in women with hypertension and various functional vascular disturbances associated with the menopause. In such a case one may make the most exhaustive clinical, electrocardiographic, and roentgenologic studies and still be in doubt as to how much of the patient's dyspnea is dependent on the organic disorder and how much is related to the oversensitive psyche. The decision is an important one because not only prognosis but treatment depends upon it.

It is in this type of patient that we believe the ventilation test gives information which cannot be obtained by any other means. In the series of 100 subjects who performed the test in the present study there were 12 such cases. By way of illustration brief abstracts of 5 of these cases are presented.

#### CASE REPORTS

A medical student had had rheumatic fever twice in childhood. During his third year in medical school he began to notice occasional palpitation and some dyspnea on climbing stairs. He was not highly neurotic but was somewhat apprehensive. Examination revealed a cardiac impulse just outside the midclavicular line. There were characteristic signs of mitral stenosis and of aortic insufficiency. The heart rate was 90; the rhythm regular. Lungs, liver, and extremities were normal.

*Clinical Diagnosis:* Chronic rheumatic endocarditis of aortic and mitral valves. Questionable mild cardiac neurosis.

Teleroentgenogram revealed slight cardiac enlargement; electrocardiograms were normal except for left axis deviation.

The values for the ventilation index were 15.1, 16.8 and 19.7 (upper normal limits 20-25-30) for the three exercises, respectively. He was reassured and told that his dyspnea was probably due to apprehension rather than to his cardiac disease. He has had no further symptoms although he leads a normal, active life.

Mrs. H. McC., aged fifty-seven years, complained of indigestion, belching, intermittent diarrhea with mucous stools, nervousness, "quivering spells," and insomnia. She suffered palpitation and dyspnea on stair climbing when nervous and when she had abdominal distention. The cardiac rate was 90; the rhythm regular. The impulse was felt 1.0 cm. outside the midclavicular line. All the cardiac sounds were somewhat accentuated. There were no murmurs. The peripheral vessels were soft. The blood pressure was 158/98 mm. The arteries were not abnormal. There was no evidence of visceral congestion and no edema. Electrocardiogram was normal. Teleroentgenogram showed a cardiac shadow at the upper limits of normal size.

*Clinical Diagnosis:* Psychoneurosis, hypertension, slight cardiac enlargement.

Despite the slight cardiac enlargement it was our impression that her cardiac symptoms were mainly due to the functional state. However, the values for the ventilation index for the three exercises were 23.0, 35.6 and 45.3 (upper normal limits 20-25-30). In view of this she was given digitalis with rapid and rather striking improvement. Several months later she omitted digitalis and, following an attack of influenza, she developed frank congestive failure.

Mr. J. B. B., aged fifty-one years, had chronic cholecystitis. He was a high-strung, introspective person, given to crying spells and had had a "nervous breakdown" several years previously. He was decidedly "heart-conscious" and often had palpitation on lying down. He had never noted dyspnea. He had had rheumatic fever when twenty-five years old. The heart was not enlarged. The rate was 90; there was an occasional premature beat. At the apex a very high-pitched musical systolic murmur was heard. This was louder with the patient sitting than when he was recumbent and the intensity was greater after exercise than at rest. There were no signs of pulmonary or systemic congestion. Peripheral vessels were soft. Blood pressure was 122/80 mm. Electrocardiogram was normal; teleroentgenogram revealed a normal sized cardiac shadow.

*Clinical Diagnosis:* Chronic cholecystitis, cardiac neurosis, mild chronic rheumatic endocarditis of mitral valve—not progressive.

The curve for the ventilation test was lower than the average for normal persons. He was reassured and given no other cardiac therapy. He has continued to have occasional palpitation but no longer fears it. He still is dyspnea-free.

Mrs. W. N. B., aged forty-eight years, complained of "hot flashes," "cold chills," nervousness, and dyspnea. She had not menstruated for six months. Since an attack of influenza thirteen years previously she had noted dyspnea on rapid walking. In the past few months she had had "choking and smothering spells" when nervous and believed that she was more dyspneic on exertion than previously. She was never dyspneic at rest except when nervous. She was considerably overweight. The maximum point of cardiac impulse was 2 cm. outside the midclavicular line. The cardiac borders were indistinct by percussion. The rate was 90; the rhythm regular. There were no murmurs. The cardiac sounds approached each other in quality. The arteries were not thickened. Blood pressure was 160/104 mm. The lungs were clear, the liver was not felt; there was

no edema. By x-ray examination the heart appeared to be just at the upper normal limit in size. The electrocardiogram revealed left axis deviation.

*Clinical Diagnosis:* Obesity, hypertension, probable cardiac enlargement, menopause, cardiac neurosis.

Values for the ventilation test were 25.3, 30.1, and 39.2 for the three exercises as compared to 20-25-30, the upper normal limits. Following digitalis and reduction of her weight, her dyspnea improved considerably.

Mrs. A. J. C., aged twenty-six years, desired to know whether it was safe for her to have a baby. When she was fourteen years old, she was told she had a heart murmur, and was instructed to limit her exercise to slow walking. She had never had any symptoms referable to the heart other than dyspnea on walking rapidly uphill. She was not neurotic. The heart was not enlarged either by physical examination or by x-ray. There was a very loud, rough systolic murmur at the pulmonic area. The pulmonic second sound was rather faint. Electrocardiogram showed right axis deviation. Fluoroscopy revealed prominence in the region of the pulmonic artery. The heart was apparently not enlarged.

*Clinical Diagnosis:* Congenital cardiac disease, either patent ductus arteriosus or pulmonic stenosis of slight degree.

The values for the ventilation index were just at the upper normal limits. She was told to have the baby if she so desired. When last heard from she had passed through a normal pregnancy and a normal labor and had had no symptoms referable to the heart.

It was our belief that in each of these cases the data obtained from the ventilation test were of some value in prognosis and treatment. As has been stated, we do not believe the method is of any great value, except as a means of research in other types of cases.

#### SUMMARY AND DISCUSSION

1. Measurements of the vital capacity and of the ventilation upon the performance of a series of standardized exercises were made on 100 subjects. Of these, 21 were normal, 16 had cardiac neurosis, 10 had organic cardiac disease without symptoms, 21 had dyspnea on exertion only, and 32 had, in addition to dyspnea on exertion, some respiratory discomfort at rest. From the measurements a value called the ventilation index, which is a fairly close objective expression of the degree of dyspnea, was calculated.

2. Analysis of the data shows that the determination of the ventilation index is of little or no value in the diagnosis of the presence or absence of organic heart disease, because patients with cardiac neurosis, patients with asymptomatic cardiac disease and normal subjects all occasionally have borderline tests, although the majority of patients in these groups have normal values. Patients with cardiac dyspnea nearly always have high values for the ventilation index but in such patients the customary methods of study are usually adequate to establish a diagnosis of the presence of organic cardiac disease.

3. In a given case repeated determinations of the ventilation index may be of considerable value in prognosis. Single tests give relatively

little information as to the outlook. In general, the patients with low values have a good prognosis and those with very high values have a poor outlook but exceptions are fairly numerous because the test only measures the degree of dyspnea at the moment, and is not influenced by such extremely important factors as the liability to infection, the tendency to thrombosis or the likelihood of coronary and other vascular accidents.

4. The ventilation test appears to be of definite clinical value in one group of cases: namely, in those patients who have both organic and functional disorders referable to the heart. Such instances are not uncommon and the ventilation test allows one to determine with fair accuracy how much of the patient's dyspnea is due to the cardiac neurosis and how much to the cardiac disease. This information, which cannot be obtained by any other method may be of considerable value in prognosis and in treatment.

5. The chief value of the ventilation test is in research, because it provides a method for determining quantitatively the effect of various therapeutic measures on dyspnea.

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## DEPRESSION OF THE VOMITING REFLEX BY THE DIGITALIS BODIES\*

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THE emetic action of the digitalis bodies has been the subject of numerous experimental investigations. These have dealt mainly with its mechanism and the conditions under which these drugs induce vomiting.<sup>1</sup> It is a very familiar phenomenon in both animals and man that a moderately toxic dose induces one or two attacks of vomiting and as the dose is increased vomiting continues and becomes more intense. There may be remissions lasting several hours; then the vomiting recurs and may continue for a day or two after the drug has been discontinued. The drug sometimes causes death in dogs and cats without having produced vomiting. After a very large intravenous injection a convulsion and death may occur within a few seconds; this does not appear to allow sufficient time for vomiting to take place. We have, however, seen cats die even after an intramuscular injection of ouabain without vomiting. Under ordinary conditions such observations are rare.

Several years ago in the course of a study of digitalis elimination, one of us<sup>2</sup> observed what appeared to be an interference with the vomiting mechanism after repeated injections of digitalis. It was noted that after small doses were injected daily intravenously in several cats there came a point when sufficient cumulation had taken place to induce vomiting. The next few daily doses continued to cause vomiting, but the last two or three daily doses before the animal died no longer produced emesis. In those experiments electrocardiograms were not taken. Such a change in the response of the vomiting reflex to the digitalis bodies might be of considerable practical importance in view of the fact that reliance is generally placed on nausea and vomiting as signs for discontinuing digitalis in order to avoid serious overdosage.

The present study was undertaken to extend these observations and to determine whether it be possible, by the repeated injections of the digitalis bodies, to diminish or abolish the emetic action of the drugs while at the same time increasing the intensity of the cardiac poisoning.

### EXPERIMENTAL

Preliminary experiments were performed on cats. Fifteen animals were given repeated intravenous injections of digitoxin, ouabain, or the tincture of digitalis until death, and the occurrence of nausea and

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vomiting after each dose was noted. No electrocardiograms were taken because cats are too excitable to permit the taking of satisfactory tracings unless they are restrained or anesthetized, and both of these procedures interfere with vomiting.

The essential results are based on a series of experiments carried out on six dogs. The digitalis bodies, digitoxin, ouabain, and the tincture of digitalis, were always injected intravenously. The size of the individual doses and the intervals were varied for every experiment. It was planned to have the individual doses\* so small as to make it possible to detect the order in which different changes might appear. On the other hand, inasmuch as the animal would usually refuse food during the experiment, it was desirable to give doses large enough so as not to prolong the experiment beyond a few days, since prolonged starvation might introduce complicating factors.

Electrocardiograms were taken at intervals before and after the injection of the drugs. Tracings were obtained at such times as to record the immediate, as well as the delayed, effects. Only Lead II was taken. The animal was allowed to sit or lie quietly on the table without anesthesia or restraint. In all more than 200 electrocardiograms were examined. The interpretation of some of the changes presented considerable difficulties, some being due to shifting of the electrical axis of the heart when the animal stood up to vomit. The T-wave, in particular, was extremely variable (Fig. 3). The only changes in the electrocardiogram that were attributed directly to the action of digitalis were extreme slowing of the sinus rate, marked depression of the R-T segment, ventricular ectopic beats, ventricular tachycardia, and A-V block.

Nausea and vomiting were regarded as signs of stimulation of the vomiting reflex. Retching was considered tantamount to vomiting, and whether vomitus was expelled or not, it is recorded as vomiting in the tables. In some cases no significance was attached to the usual signs of nausea because the experiment was carried out during very hot weather when the animal often panted, licked, and swallowed even when drugs were not given. The occurrence of vomiting during the night could be detected the following morning by a pool of vomitus. It is possible that retching (without the expulsion of vomitus) could have occurred during the night in the case of some animals recorded as having failed to vomit after a given injection. We have, nevertheless, recorded it as a failure to vomit in cases in which vomiting did not occur for some hours of observation after the intravenous injection and in which no evidence of it was detected the following morning. Occasionally an animal may vomit for the first time a few hours after the intravenous injection of the digitalis bodies; especially is this so in

\*All doses were given in milligrams per kilogram but "per kilogram" is omitted in the text for the sake of brevity.

the case of digitoxin. Nevertheless, the change in the behavior of the vomiting reflex after repeated injections is sufficiently striking to illustrate the matter under investigation.

The development of "conditioned" vomiting demanded some attention since the animals were made to vomit from drugs at the same place and under the same conditions for several days in succession. We have found that some dogs develop this conditioned reflex after a few days, which may then persist for months. An animal so "conditioned" may begin to lick and swallow when placed on the table and may vomit by the time the electrodes are applied. In these experiments, therefore, the animals were allowed to remain on the table for some time before the injections were made in order to detect such reactions.

#### RESULTS

The experiments on cats will not be reviewed in detail inasmuch as there were no electrocardiographic records of cardiac changes. With the doses used five of the fifteen experiments demonstrate definite interference with the vomiting reflex after repeated injections of the digitalis bodies. The different experiments varied widely in the number, the size, and the intervals between the individual doses. The following condensed protocol of one experiment will illustrate, however, the type of reaction from which it was deduced that an interference with the vomiting reflex had occurred.

Cat, female, weight 1.32 kg.

##### October 8

|      |  |
|------|--|
| 2:48 | 0.1 mg. digitoxin per kg. intravenously. |
| 2:50 | Falls on side.                           |
| 3:13 | Nausea.                                  |
| 3:15 | Vomits.                                  |
| 5:20 | Has vomited seven times.                 |

##### October 10

|      |  |
|------|--|
| 2:35 | Slight depression; drinks water.         |
| 2:37 | 0.1 mg. digitoxin per kg. intravenously. |
| 3:03 | Vomits.                                  |
| 3:47 | Vomits.                                  |
| 3:57 | General depression.                      |

##### October 11

|       |  |
|-------|--|
| 12:54 | Slight depression; drinks water.                     |
| 1:03  | 0.03 mg. digitoxin per kg. intravenously.            |
| 1:26  | Refuses water and meat.                              |
| 3:10  | General depression but able to stand and walk about. |
| 6:30  | Still no vomiting; general condition same.           |

##### October 12

|      |   |
|------|---|
| 9:00 | Found dead this morning. No signs of vomiting during night. Autopsy—no evidence of infection. |
|------|---|

Of the six experiments with dogs the results in five will be presented in some detail in order to convey an idea of the variety of conditions under which the phenomenon under consideration may appear. Summaries are given in Tables I to V. In the case of the sixth animal, vomiting occurred after each of the three daily injections of digitalis and fifteen minutes after the last dose the respiration ceased, although the heart continued to beat while artificial respiration was maintained for an hour. This behavior is atypical and does not show any interference with the vomiting reflex.

TABLE I

| DATE   | TIME | DOSE<br>PER CENT OF FATAL          |       | NAUSEA<br>AND<br>VOMITING | ONSET<br>IN<br>MINUTES | CARDIAC CHANGES  |
|--------|------|------------------------------------|-------|---------------------------|------------------------|--|
|        |      | SINGLE                             | TOTAL |                           |                        |  |
| May 8  | 3:06 | 33                                 | 33    | Vomiting                  | 13                     | Temporary change in focus of pacemaker                 |
| May 9  | 3:31 | 17                                 | 50    | Nausea<br>No vomiting     | 1                      | Normal rhythm  |
|        | 4:14 | 17                                 | 67    | Vomiting                  | 11                     | Bradycardia  |
|        | 4:51 | Apomorphine HCl<br>0.5 mg., muscle |       | No vomiting               | --                     | Sinus tachycardia →<br>ventricular tachycardia         |
| May 10 | 5:09 | Apomorphine HCl<br>1.0 mg., muscle |       | Nausea?<br>No vomiting    | --                     | Sinus tachycardia                                      |
|        | 3:08 | --                                 | --    | --                        | --                     | Normal rhythm,<br>slight depression of<br>R-T segment  |
|        | 3:09 | Apomorphine HCl<br>0.5 mg., muscle |       | Nausea<br>No vomiting     | 2                      | Sinus tachycardia                                      |
|        | 3:25 | 17                                 | 84    | No vomiting               | --                     | Rhythm normal,<br>greater depression<br>of R-T segment |
|        | 3:39 | 17                                 | 100   | Vomiting                  | 4                      | Bradycardia → ven-<br>tricular tachycardia             |
|        | 9:00 | --                                 | --    | --                        | --                     | Found dead   |

Dog, male, 7.0 kg. Tr. digitalis was used diluted with an equal volume of normal saline solution after evaporation of alcohol with moderate heat. Doses are stated above in percentage of the total fatal dose for this animal.

EXPERIMENT I.—This experiment lasted three days; the results are presented in Table I. Thirty electrocardiograms were taken during this period, ten of which are reproduced in Fig. 1, and represent the essential cardiac changes. On the first day, one-third of the total dose of digitalis which proved fatal for this animal was injected intravenously. This produced vomiting but no persistent changes in the electrocardiogram (Tracings 1 and 3). The following morning the dog appeared fairly normal, but was still nauseated and refused food and water. A second injection consisting of one-sixth of the fatal dose was made, which caused slowing of the sinus rate and marked nausea but no vomiting (Tracing 11). After a third injection, one-sixth of the fatal dose, the animal became very ill; there was profound slowing of the heart rate, severe nausea, repeated vomiting, respiratory distress, and excitement. When this disturbance had partially subsided, the electrocardiogram appeared practically as it had before any digitalis had been given (Tracing 16). On the morning of the third day the animal was only slightly depressed. An injection of digitalis, one-sixth of the fatal dose, caused a marked depression of the R-T segment but no nausea or vomiting (Tracing 25), although by now a total of 84 per cent of the fatal dose of the drug had been

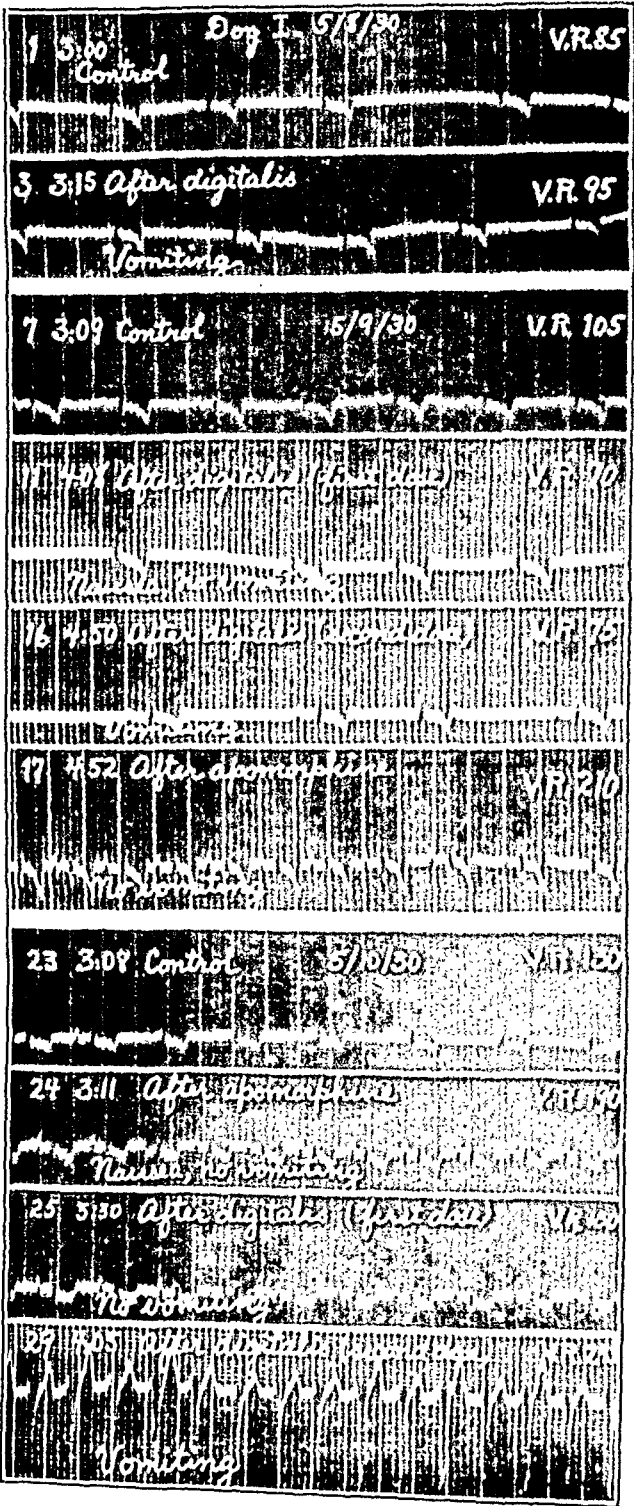


Fig. 1.

given. The repetition of this dose resulted in the same type of symptoms as occurred after the second dose on the day previous, namely, repeated vomiting, marked respiratory distress, and depression. In addition, however, a ventricular tachycardia was now produced (Tracing 29). The animal was found dead the following morning, and autopsy showed no signs of infection.

Repeated injections of digitalis, therefore, produced progressively increasing poisoning of the heart which was not consistently reflected in the symptom of vomiting. For example, after 33 per cent of the fatal dose vomiting occurred, but the R-T segment was not altered; while after 84 per cent, vomiting was absent although this amount of digitalis was sufficient to produce marked depression of the R-T segment.

After 67 per cent of the fatal dose of digitalis had been given, 1.5 mg. apomorphine then failed to cause emesis, and 0.5 mg. apomorphine before the digitalis on the following day was also ineffective. Since the average minimum intramuscular emetic dose of apomorphine in the dog is about 0.02 mg., there can be no question of the increased threshold of the vomiting reflex to apomorphine in this case. That the apomorphine had been rapidly absorbed is evident from the fact that the injection was followed in two minutes by marked acceleration of the heart rate (Tracings 17 and 24) while the animal was lying perfectly quiet.

TABLE II

| DATE   | TIME  | DOSE                                | NAUSEA<br>AND<br>VOMITING | ONSET<br>IN<br>MINUTES | CARDIAC CHANGES                          |
|--------|-------|-------------------------------------|---------------------------|------------------------|--|
| May 9  | 11:48 | 60% c.u. Digitalis                  | Nausea                    | 1                      | Normal rhythm                            |
|        |       |                                     | Vomiting                  | 5                      |  |
| May 11 | 10:15 | Apomorphine HCl<br>0.25 mg., muscle | Vomiting                  | 4                      | Normal rhythm                            |
| May 19 | 2:57  | Ouabain<br>0.05 mg., vein           | Nausea                    | 2                      | Ventricular<br>tachycardia               |
|        | 4:00  | Apomorphine HCl<br>0.25 mg., muscle | Vomiting                  | 4                      | Ventricular<br>tachycardia               |
| May 20 | 12:00 | --                                  | --                        | --                     | Sinus tachycardia                        |
|        | 12:20 | Ouabain<br>0.05 mg., vein           | No nausea<br>No vomiting  | --<br>--               | Ventricular tachycardia in three minutes |
|        | 12:37 | --                                  | --                        | --                     | Convulsion; death                        |

Dog, female, 24.8 kg. c.u. (cat units). Tincture digitalis was used, diluted with an equal volume of normal saline after the alcohol was evaporated off with moderate heat. A solution of ouabain in normal saline 1 in 1000 was used.

EXPERIMENT II.—The results of this experiment are summarized in Table II. Twenty-five electrocardiograms were taken, and the essential tracings are reproduced in Fig. 2. The first dose of digitalis induced salivation and vomiting in five minutes, and after a temporary sinus tachycardia (Tracing 3), the electrocardiogram became entirely normal (Tracing 7). Subsequently 0.05 mg. ouabain caused vomiting in eight minutes and, in addition, a ventricular tachycardia (Tracing 17). The following day the dog refused food but took a large quantity of water which was promptly regurgitated. There was no further nausea or vomiting, although salivation appeared before the next injection. The animal was somewhat less lively than normal but not markedly depressed. There was a sinus tachycardia (Tracing 22). After the dose of ouabain on this day respiration remained unchanged, slight drowsiness was induced, and a ventricular tachycardia appeared (Tracings 23 to 25) which progressed to ventricular fibrillation. This, in turn, was followed by a convulsion and death. The last dose of ouabain had produced a toxic action on the

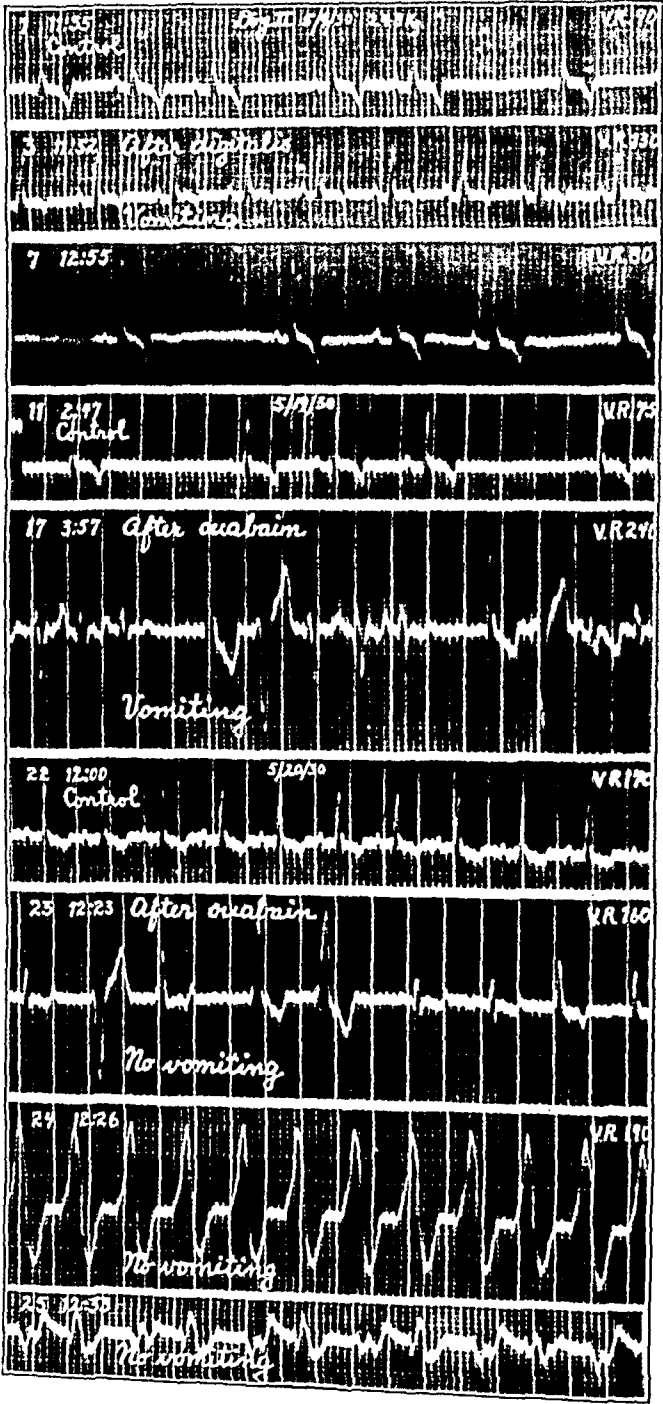


Fig. 2.

heart without the slightest signs of nausea or vomiting although seventeen minutes had elapsed between the injection and death.

The first injection of ouabain caused vomiting five times in a period of thirty-five minutes. An intramuscular injection of 0.25 mg. apomorphine given twenty-five minutes later promptly produced vomiting which recurred six times. This response was essentially the same as that obtained by a previous control injection of apomorphine.

TABLE III

| DATE   | TIME  | SINGLE DOSE MG./KG.              | TOTAL DOSE IN % OF FATAL | NAUSEA AND VOMITING           | ONSET IN MINUTES | CARDIAC CHANGES  |
|--------|-------|----------------------------------|--------------------------|-------------------------------|------------------|--|
| May 20 | 4:41  | 0.025                            | 16.7                     | Nausea                        | 1                | Normal rhythm  |
|        | 4:54  | 0.025                            | 32.4                     | Nausea                        | 1                | Normal rhythm  |
|        |       |                                  |                          | Vomiting                      | 4                |  |
| May 21 | 12:11 | 0.025                            | 49.1                     | Nausea                        | 5                | Normal rhythm  |
|        |       |                                  |                          | Vomiting                      | 6                |  |
|        | 3:15  | 0.025                            | 65.8                     | Vomiting (atypical)           | 11               | Ventricular tachycardia  |
| May 22 | 9:00  | --                               | --                       | --                            | --               | Periods of ventricular tachycardia, sinus tachycardia, prolonged P-R intervals |
|        | 9:45  | 0.008                            | 71.1                     | No nausea<br>No vomiting      | --<br>--         | Same as above  |
|        | 1:41  | 0.008                            | 76.4                     | No nausea<br>No vomiting      | --<br>--         | Sinus bradycardia, ventricular ectopic beats                                   |
|        | 2:04  | 0.008                            | 81.7                     | Nausea<br>Vomiting (atypical) | 3<br>5           | Ventricular tachycardia  |
|        | 2:51  | Apomorphine HCl 0.25 mg., muscle |                          | Nausea<br>Vomiting            | 2<br>6           | Ventricular tachycardia  |
|        | 9:39  | --                               | --                       | --                            | --               | Ventricular tachycardia  |
|        | 9:43  | 0.008                            | 87.0                     | No nausea<br>No vomiting      | --<br>--         | Ventricular tachycardia  |
| May 23 | 10:23 | 0.006                            | 91.0                     | No nausea<br>No vomiting      | --<br>--         | Ventricular tachycardia  |
|        | 10:35 | 0.012                            | 100.0                    | No nausea<br>No vomiting      | --<br>--         | Ventricular tachycardia  |
|        | 10:55 | --                               | --                       | --                            | --               | Ventricular fibrillation; convulsion; death                                    |

Dog, male, 12.7kg. A solution of ouabain in normal saline 1 in 1000 was used.

EXPERIMENT III.—The duration of this experiment was four days during which thirty-three electrocardiograms were taken. The results are summarized in Table III and the essential tracings given in Fig. 3.

The first dose of ouabain (16.7 per cent of the fatal) caused nausea, and the same dose given thirteen minutes later induced vomiting in four minutes, which was repeated ten times in the following thirty-seven minutes. The electrocardiograms of this day showed no abnormal rhythm (Tracings 2 and 6), and the animal showed no depression.

The following morning it was evident that the animal had vomited several times during the night. Food was refused, but the dog drank a large quantity of water and appeared fairly normal. The electrocardiogram showed an essentially normal rhythm (Tracing 11) which remained unchanged after the next injection of ouabain (16.7 per cent of the fatal dose) (Tracing 14). This dose also caused vomiting which was repeated six times. The repetition of this dose nearly two hours after vomiting had stopped produced a ventricular tachycardia (Tracing 17), in addition



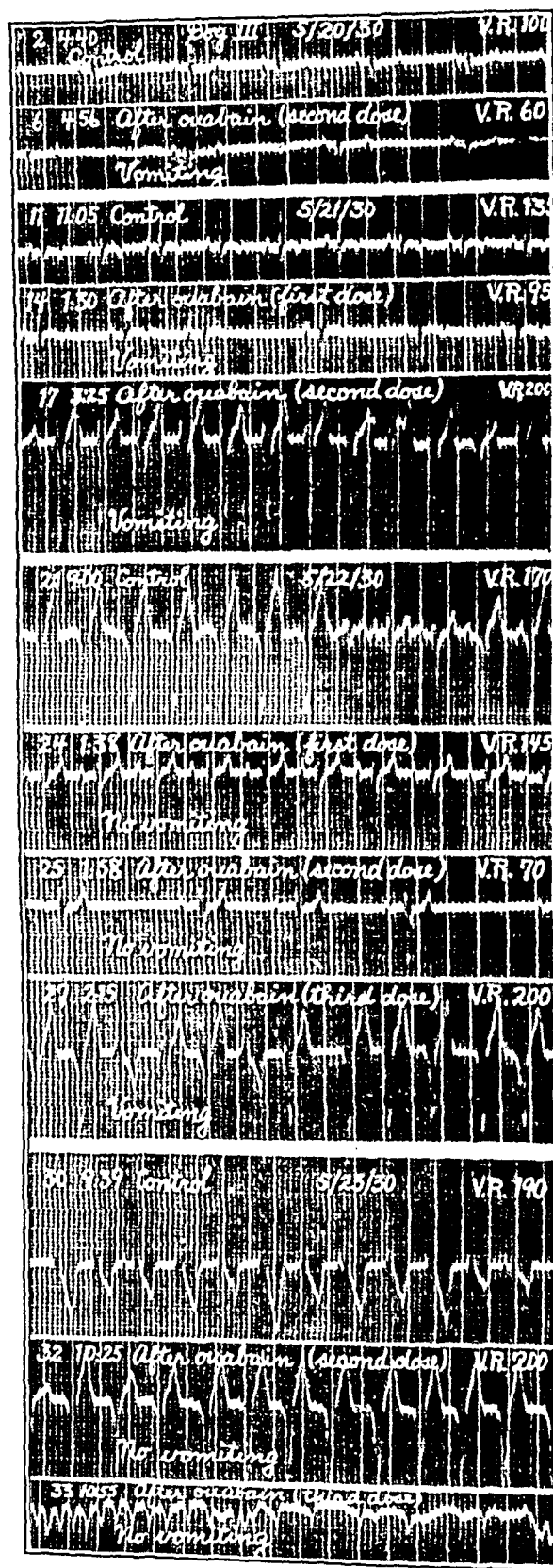


Fig. 3.

to a severe generalized disturbance that was characterized by slow, deep, and gasping respiration and violent excitement in which the animal threw itself about and cried out. Repeated atypical retching movements ensued. Considerable restlessness and marked weakness lasted for more than an hour and a half, after which the animal showed improvement and drank a large amount of water.

On the morning of the third day, there was no evidence of vomiting during the night. The animal appeared slightly weak, but again drank a large quantity of water. The electrocardiogram showed long periods of ventricular tachycardia (Tracing 21). Two doses of ouabain (each 5.3 per cent of the fatal) produced further cardiac changes but no vomiting (Tracings 24 and 25). A third dose induced an attack similar to that on the previous day, with extreme respiratory distress and atypical retching (Tracing 27). After partial recovery from this, the animal was capable of vomiting from apomorphine.

On the morning of the fourth day, there was again no sign of vomiting during the night. The animal was slightly depressed, and drank a considerable quantity of water but refused food. The electrocardiogram showed ventricular tachycardia (Tracing 30). Three doses of ouabain were injected but produced neither vomiting nor even signs of nausea. The last of these doses caused another severe attack of excitement and respiratory distress, the animal biting at the chain, clawing violently at its mouth, belching, and grunting. There was partial recovery in about fifteen minutes, but as the animal was lifted from the floor and placed on the table, a convulsion occurred and the electrocardiogram showed ventricular fibrillation (Tracing 33). On this day, although a dose of ouabain had been given which produced fatal poisoning of the heart, there was neither nausea nor vomiting.

TABLE IV

| DATE    | TIME  | DOSE<br>MG./KG.                     | VOMITING    | ONSET<br>IN<br>MINUTES | CARDIAC CHANGES           |
|---------|-------|-------------------------------------|-------------|------------------------|---------------------------|
| June 6  | 1:49  | 0.10                                | Vomiting    | 26                     | Normal rhythm             |
|         | 3:48  | 0.05                                | Vomiting    | 12                     | Normal rhythm             |
| June 7  | 10:15 | 0.05                                | No vomiting | --                     | Normal rhythm             |
|         | 11:10 | 0.05                                | Vomiting    | 7                      | Normal rhythm             |
| June 9  | 1:50  | 0.10                                | No vomiting | --                     | Normal rhythm             |
|         | 2:52  | 0.10                                | Vomiting    | 8                      | Normal rhythm             |
| June 10 | 11:21 | 0.10                                | No vomiting | --                     | Normal rhythm             |
|         | 12:57 | 0.05                                | No vomiting | --                     | Normal rhythm             |
|         | 2:17  | 0.10                                | No vomiting | --                     | Normal rhythm             |
|         | 3:47  | 0.10                                | No vomiting | --                     | Ventricular ectopic beats |
|         | 4:40  | Apomorphine HCl<br>1 mg., muscle    | Vomiting    | 3                      | Normal rhythm             |
| June 11 | 12:14 | 0.15                                | No vomiting | --                     | Ventricular ectopic beats |
|         | 1:33  | 0.15                                | No vomiting | --                     | Ventricular ectopic beats |
|         | 2:34  | 0.15                                | No vomiting | --                     | Ventricular tachycardia   |
|         | 3:34  | Apomorphine HCl<br>0.25 mg., muscle | No vomiting | --                     | Ventricular tachycardia   |
|         | 3:50  | Apomorphine HCl<br>0.25 mg., vein   | No vomiting | --                     | Ventricular tachycardia   |
|         | 4:00  | Apomorphine HCl<br>0.50 mg., muscle | Vomiting    | 3                      | Ventricular tachycardia   |
| June 12 | 11:25 | 0.15                                | Vomiting    | 49                     | Ventricular tachycardia   |
|         | 3:35  | Picrotoxin-like<br>convulsions      | ----        | --                     | Ventricular tachycardia   |
|         | 4:10  | Death                               |             |                        |                           |

Dog, male, 18.2 kg. A solution of Digitoxin-Merck was used, containing 10 mg. in 1 c.c. alcohol and diluted ten times with normal saline for injection.

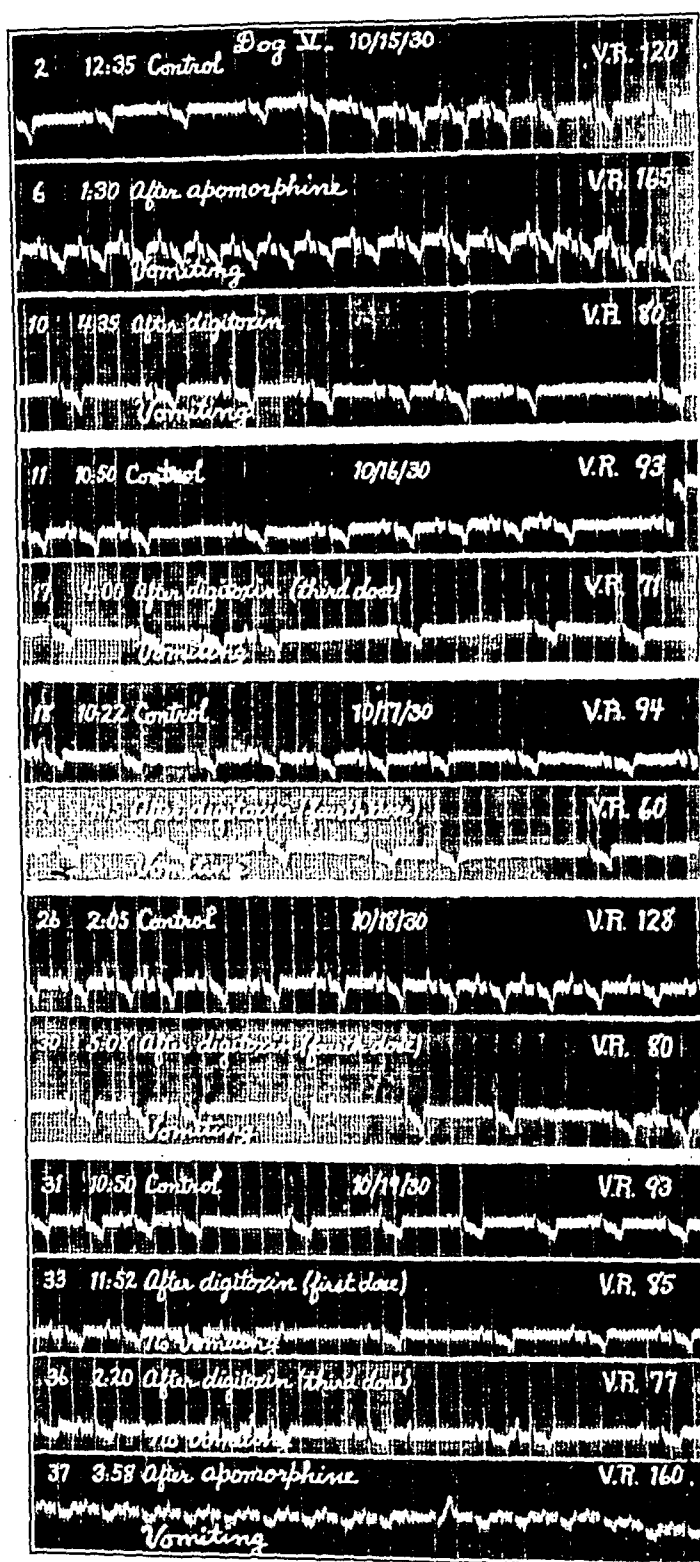


Fig. 4.

EXPERIMENT IV.—In this experiment fifty-five electrocardiograms were taken. None are reproduced, since the tracings are essentially the same as those of Experiment III. The relation between the repeated injections of digitoxin and the occurrence of vomiting is shown in Table IV. It may be seen that emesis occurred after the total dose given on each of the first three days (June 6, 7, and 9). On the next two days (June 10 and 11) even larger doses failed to cause vomiting, although a greater toxic action on the heart was in evidence, namely, ventricular tachycardia. On the following day (June 12) an injection caused vomiting and death. Thus, a progressive increase in the threshold of the vomiting mechanism is shown. On the first day, 0.1 mg. digitoxin caused vomiting. On the third day (June 9), 0.1 mg. was no longer effective, while 0.2 mg. still induced emesis. On the fourth day, even after 0.35 mg., vomiting did not occur. On the fifth day, 0.45 mg. was also insufficient to cause vomiting. On the last day, a dose of 0.15 mg. produced vomiting, but by this time sufficient cumulation had taken place for this small dose to cause death.

TABLE V

| DATE    | TIME  | DOSE<br>MG./KG.                   | NAUSEA AND<br>VOMITING | ONSET IN<br>MINUTES | CARDIAC CHANGES             |
|---------|-------|-----------------------------------|------------------------|---------------------|-----------------------------|
| Oct. 15 | 1:15  | Apomorphine HCl<br>0.05 mg., vein | Nausea                 | 1                   | Sinus tachycardia           |
|         |       |                                   | Vomiting               | 1                   |                             |
|         | 3:21  | 0.10                              | Nausea                 | 3                   | Sinus slowing               |
|         |       |                                   | Vomiting               | 34*                 |                             |
| Oct. 16 | 11:00 | 0.05                              | No nausea              | --                  | Sinus slowing               |
|         |       |                                   | No vomiting            | --                  |                             |
|         | 11:58 | 0.05                              | Nausea                 | 1                   | Sinus slowing               |
|         |       |                                   | Vomiting               | 44                  |                             |
| Oct. 17 | 1:48  | 0.05                              | Nausea                 | ½                   | Sinus slowing               |
|         |       |                                   | Vomiting               | 2                   |                             |
|         | 10:30 | 0.05                              | Nausea                 | 1                   | Normal rhythm               |
|         |       |                                   | No vomiting            | --                  |                             |
| Oct. 18 | 12:05 | 0.05                              | No nausea              | --                  | Sinus slowing               |
|         |       |                                   | No vomiting            | --                  |                             |
|         | 1:10  | 0.05                              | Nausea                 | 5                   | Sinus slowing               |
|         |       |                                   | Vomiting               | 6                   |                             |
| Oct. 18 | 2:10  | 0.05                              | Vomiting               | 130†                | Sinus slowing               |
|         | 2:07  | 0.05                              | No nausea              | --                  | Sinus slowing               |
|         |       |                                   | No vomiting            | --                  |                             |
|         | 3:07  | 0.05                              | No nausea              | --                  | Sinus slowing               |
| Oct. 18 |       |                                   | No vomiting            | --                  |                             |
|         | 4:07  | 0.05                              | Nausea                 | 3                   | Sinus slowing               |
|         |       |                                   | Vomiting               | 4                   |                             |
|         | 4:52  | 0.10                              | Nausea                 | 3                   | Dropped beats               |
| Oct. 18 |       |                                   | Vomiting               | 23‡                 |                             |
|         | 10:53 | 0.10                              | Nausea                 | 47                  | Dropped beats               |
|         |       |                                   | No vomiting            | --                  |                             |
|         | 12:00 | 0.05                              | Nausea                 | 25                  | Dropped beats               |
| Oct. 18 |       |                                   | No vomiting            | --                  |                             |
|         | 1:12  | 0.05                              | Nausea                 | 6                   | More frequent dropped beats |
|         |       |                                   | No vomiting            | --                  |                             |
|         | 3:00  | Apomorphine HCl                   | Nausea                 | 3                   | Sinus tachycardia with      |
| Oct. 19 |       | 0.05 mg., vein                    | Vomiting               | 23                  | A-V block                   |

Dog, male, 7.6 kg. A solution of Digitoxin-Merck was used, continuing 10 mg. in 1 c.c. alcohol and diluted ten times with normal saline for injection.

\*After preliminary nausea ate meat ravenously and then had nausea and vomiting twenty minutes later.

†In this case there were no signs of nausea or vomiting while the animal was lying on the table, but when placed on the floor, it vomited almost instantly.

‡Vomited again only after being placed on the floor, not while sitting on the table. Neither in this case nor in that above was the animal lying on its back, nor in any way restrained.

When the animal began to show resistance to the emetic action of digitoxin, it was also resistant to that of apomorphine. An intramuscular injection of 0.25 mg. apomorphine and a similar dose given intravenously sixteen minutes later proved ineffective. An additional dose of 0.5 mg. intramuscularly produced vomiting in three minutes.

EXPERIMENT V.—This experiment was conducted for five days. Thirty-seven electrocardiograms were taken. The essential facts are summarized in Table V and illustrated by the tracings in Fig. 4. The animal vomited from the digitoxin injections on each of the first four days but failed to do so after the digitoxin on the fifth day. So far as the cardiac poisoning is concerned, the dose that produced vomiting on the first day was insufficient to cause heart-block (Tracing 10). On the other hand, vomiting was absent on the fifth day after a total quantity of the drug that was sufficient to produce heart-block (Tracings 33, 36, and 37). It is interesting to compare Tracings 6 and 37. Each shows the sinus tachycardia following apomorphine. Tracing 6, however, is otherwise normal, the P-R intervals being 0.04 to 0.06 second, while Tracing 37 shows in addition to the sinus tachycardia a marked toxic action of digitoxin, namely, P-R intervals 0.10 to 0.12 second, dropped beats, a ventricular ectopic beat, and marked depression of the R-T segment. After Tracing 6, digitoxin produced emesis without any electrocardiographic signs of toxicity, while at the time that Tracing 37 was taken there was marked resistance to the emetic action of digitoxin.

#### DISCUSSION

The experiments of the present study set forth the fact that after repeated doses of the digitalis bodies the vomiting reflex in the dog and the cat shows a change in the reaction to the drug. This change is such that a dose previously effective in producing vomiting becomes ineffective. The cardiac poisoning continues to increase progressively with the repeated doses so that ultimately a toxic rhythm without emesis is induced by an additional dose of the drug which at the beginning of the experiment caused vomiting without the toxic rhythm. This is perhaps the most significant fact of this study, because vomiting is generally relied upon clinically as a signal for the discontinuation of the drug in order to avoid serious cardiac poisoning.

The explanation of the foregoing phenomenon brings up many possibilities, such as (1) fatigue of the vomiting reflex due to prolonged vomiting, (2) general depression of the animal, (3) suppression of the vomiting reflex by a stronger impulse arising from the sudden disorder of the cardiac rhythm, (4) differences in the degree of fixation of the drug by different structures, (5) the development of tolerance to digitalis by the structures concerned with vomiting, (6) direct depression of the vomiting reflex by the digitalis bodies.

Fatigue of the vomiting reflex as the result of prolonged vomiting suggested itself because toxic doses of digitalis cause very severe vomiting that may last several hours and even days. In some cases, the animal vomited as many as ten or fifteen times after each injection. It is well known, however, that the vomiting reflex recovers very

rapidly. Patients are often seen to vomit many times daily for weeks without signs of fatigue of this reflex, and in experiments with the daily injection of apomorphine in dogs we have seen no sign of fatigue of this mechanism after vomiting many times following each dose for a period of ten days or longer.

General depression of the animal can be dismissed as playing no rôle of importance in the failure to produce vomiting by digitalis in these experiments. When the heart was poisoned by large doses of the drug and the animal had refused food for three or four days, there was some weakness and general depression. At the time when the reflex began to show a change in its response to the drug, however, the general depression was in no case extreme, for the animals could stand up and walk about and in some instances drank water.

It seemed possible that an abnormal impulse arising from the heart as the result of the sudden onset of an extremely toxic cardiac rhythm might interfere with the vomiting reflex, for there are many familiar examples of the suppression of one reflex act by another. This factor, however, could not have played any considerable rôle in these experiments because in some instances severe disorders of cardiac rhythm occurred before the animal showed any interference with the vomiting reflex, while in other cases interference with this reflex was observed before any serious disorder of cardiac rhythm was in evidence.

That differences in the degree of fixation of the drug by different cardiac structures might be an explanation of the above phenomenon was suggested particularly by the observations of Experiment I. In this case the first dose consisting of 33 per cent of the fatal, induced vomiting. On each of the next two days approximately the same doses were necessary to induce vomiting. The fact that the animal died after the third day shows that progressive cumulation had taken place. But the fact that the same dose was required each day to induce vomiting suggested further that cumulation was not taking place in the structures concerned with the vomiting reflex. This view, however, becomes untenable in the light of the well-known fact that vomiting from a large dose of digitalis may last for hours and even days. It would fail to explain the fact that in some instances after repeated injections, single doses larger than those which at first caused vomiting now failed to produce it.

The development of tissue tolerance by some structure of the vomiting reflex would explain the observation that larger doses of digitalis become necessary to induce vomiting after repeated injections. There is no evidence, however, that any other cardiac structure can develop tolerance to digitalis. Furthermore, it would be extraordinary if a specific tolerance developed to digitalis were to extend to such a totally

different drug as apomorphine, inasmuch as the animal rendered resistant to digitalis may also become resistant to apomorphine.

The most probable explanation of the change in the response of the vomiting reflex appears to be that repeated cumulative doses of digitalis may continue to increase the cardiac poisoning while at the same time directly depressing the vomiting reflex. This rise in the threshold of the vomiting reflex may entirely abolish the emetic action of further doses of the drug (Tables II and III). An effort was made to determine whether this elevation of the threshold to stimulation might be induced by repeated small doses without ever causing vomiting, until a fatal dose had been injected, in somewhat the same way as morphine in small repeated doses may depress the vomiting center without ever causing vomiting. We cannot state whether this is possible in the case of the digitalis bodies, for with the doses employed in these experiments vomiting always occurred for the first time after the administration of only small fractions of the total quantities that proved fatal in the course of several days.

The increase in the threshold to stimulation by digitalis is not specific for that drug, but applies also to apomorphine. In Experiment I, seventy-five times the minimal emetic dose of apomorphine given intramuscularly failed to cause vomiting at a time when the animal had become resistant to vomiting by digitalis. In Experiment IV, when the vomiting mechanism became resistant to digitoxin so that nearly five times the previous emetic dose was ineffective, the animal was still capable of vomiting promptly from apomorphine. In this case, however, much larger doses than normally were required, for about twelve times the minimal intramuscular emetic dose and more than twelve times the minimal intravenous emetic dose given sixteen minutes later failed to cause vomiting. In the remaining experiments there was no evidence of increased tolerance to apomorphine. The doses, however, were too large to permit the detection of slight degrees of tolerance if any had developed. The fact that in two experiments the animals failed to vomit from such large doses of apomorphine leaves little doubt that repeated injections of the digitalis bodies rendered the reflex resistant to stimulation not only by these drugs but by apomorphine as well.

Our experiments afford no direct evidence for the exact seat of this depression of the vomiting reflex. In view of the recent studies<sup>3</sup> which indicate that digitalis vomiting results from stimulation of peripheral endings in the heart, it seems probable that the depression of this reflex is also due to a peripheral action. The fact that the depression applies to apomorphine as well indicates that not only the cardiac fibers, but also other peripheral fibers are depressed by digitalis. Hatcher and Weiss<sup>4</sup> have shown that the digitalis bodies may stimulate peripheral nerve fibers other than those in the heart.

In man, gastrointestinal disturbances are usually the first indications of digitalis poisoning. It is not uncommon, however, for abnormal cardiac rhythms (premature beats, bigeminy, block) to appear as the initial signs of toxicity. It is also observed that patients who are receiving large doses of digitalis die occasionally under conditions which suggest that the drug may have been responsible for the fatality, although nausea and vomiting were absent. For example, in the recent study on digitalis therapy in lobar pneumonia reported by Wyckoff, Du Bois, and Woodruff,<sup>5</sup> it was found that patients receiving digitalis showed a higher mortality (41.4 per cent) than those who were not treated with the drug (33.7 per cent), and furthermore, that the highest mortality (64.2 per cent) occurred in that group which at no time showed nausea or vomiting, although very large doses of the drug were administered. This observation is not strictly analogous to those of the present experiments, although it is conceivable that the pneumonia or the large doses of the drug or both, may have produced depression of the vomiting reflex which rendered it resistant to the usual action of digitalis. As we have already mentioned, animals have occasionally been observed to die without vomiting following a single large intramuscular injection of ouabain.

The clinical observations that bear more closely upon the results of the present study are the following: patients sometimes vomit from the toxic action of digitalis, and then as the drug is continued, vomiting ceases and other toxic effects appear in the form of frequent premature contractions or a bigeminal rhythm. There are several possible explanations for such changes. It is probable that active carditis and the progressive myocardial failure of the terminal stages of heart disease, both of which render the heart more susceptible to toxic rhythms produced by digitalis,<sup>6</sup> may explain these observations in some instances. The experiments of the present study deal with intense poisoning of the heart and it is not possible at present to state how frequently such conditions are duplicated in the clinical use of the digitalis bodies. It will, however, be well to bear in mind the fact established in these animal experiments, that the continued administration of large doses of these drugs may depress the vomiting reflex while progressively increasing the intensity of the cardiac poisoning, and that, after an initial period of vomiting under these conditions the digitalis bodies may even cause death without further vomiting.

#### CONCLUSION

Repeated doses of the digitalis bodies may depress the vomiting reflex while simultaneously increasing the intensity of the cardiac poisoning, so that after an initial period of vomiting the continued administration of these drugs may fail to produce emesis and may even



cause death without further vomiting. These experimental results suggest the need of caution in relying upon nausea and vomiting as measures of the degree of cardiac poisoning in the clinical use of the digitalis bodies.

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## EOSINOPHILIA DUE TO THE ADMINISTRATION OF DIGITALIS\*

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**I**N THE foreign literature, a few cases have been reported in which the administration of digitalis or its derivatives has been associated with a definite increase in the number of eosinophiles in the circulating blood.

Recht<sup>1</sup> records the study of a series of patients who had received digitalis (the powdered leaf and digipuratum) to the point of producing nausea, bradycardia, and other minor toxic symptoms. He states that on the average an eosinophilia of 6 to 8 per cent was observed. There were, however, in his series two outstanding cases which showed an eosinophilia of 18 to 20 per cent and 12 per cent, respectively. The first of these was a woman of fifty-six years with congestive heart failure who had been without digitalis for four weeks before admission to the hospital. Her eosinophile count on admission is not stated. She was given large doses of digitalis, and on the second day after admission, had an eosinophile count of 18 to 20 per cent. At this time digestive disturbances, bradycardia, and bigeminy indicated cessation of digitalis administration. While digitalis was withheld, the eosinophile count dropped gradually to 5 or 6 per cent, and remained at this level for several weeks. After two months, it was again necessary to give digitalis. The eosinophile count increased slowly to 9 per cent and at the end of three weeks reached 12 per cent. The second case, similarly treated, showed a maximum count of 12 per cent under digitalis therapy. Recht attributes this increase of eosinophile cells in the blood to the stimulation of the vagus or autonomic nervous system by the vagotropic drug, digitalis. Other causes for eosinophilia were considered to have been excluded in his cases.

Braun<sup>2</sup> reports a case of congestive failure with edema, in which an "eosinophilia" the degree of which is not stated, occurred during digitalis administration. Braun attributes this to a foreign protein reaction due to absorption of the edema fluid.

On the other hand, N. Diakoff<sup>3</sup> in a recent report on the therapeutic efficiency of some digitalis grown in Perm, states that while the samples showed satisfactory therapeutic activity, there was no occurrence of eosinophilia in the 14 cases which were studied during administration of the drug.

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The following case of eosinophilia associated with digitalis administration occurred under our observation.

## CASE REPORT

The patient was a negro male, thirty-six years old, admitted to the Out-patient Department for the first time in June, 1929. He complained of shortness of breath, cough, and precordial pain. He had had measles and mumps in childhood, and pneumonia in 1926. He had had an attack of rheumatic fever at the age of seven years, and a similar attack each winter until the age of twenty-one. There had been no severe attacks of rheumatism since that time. In February, 1929, nine months before admission, he had an attack of fever with painful and swollen joints, became short of breath, and developed a productive cough. In April, 1929, he began to have edema of the ankles and was in bed for a month. He had been vomiting 1 to 3 times a day, and had had nocturia 3 or 4 times a night.

In June, 1929, he entered the Out-patient Department and was treated with digitalis and bed rest at home. He improved temporarily, but after four months developed decompensation and was referred to the hospital.

On October 14, when he entered the hospital, his physical examination showed the heart to be enlarged to the sixth left intercostal space and outside the mid-clavicular line. There was a blowing systolic murmur at the apex. No diastolic murmur could be heard. The cardiac rhythm was totally irregular with a pulse deficit of 35 beats per minute; B.P.  $\frac{120-90}{70}$ . There were râles scattered throughout the lungs. The liver was felt 1 or 2 finger breadths below the costal margin. There was no edema of the extremities.

With bed rest and digitalis in usual amounts, he seemed to regain compensation, though the cough persisted. He was discharged on October 26.

The laboratory findings on this admission were:

|                    |          |
|--------------------|----------|
| White blood cells  | 10,600   |
|                    | PER CENT |
| Polymorphonuclears | 67       |
| Lymphocytes        | 28       |
| Transitional cells | 4        |
| Eosinophiles       | 0        |
| Unclassified       | 1        |
| Wassermann         | negative |

He was admitted to the hospital again, one month later. The cough was more severe and there were ascites and edema. He was again treated with digitalis and bed rest. At this time a low diastolic murmur was heard along the left sternal margin. He remained in the hospital until December 18 when he was transferred to another hospital in which he stayed until March, 1930.

The differential blood count on the second admission was:

|                   |          |
|-------------------|----------|
| White blood cells | 7,260    |
|                   | PER CENT |
| Basophiles        | 1        |
| Eosinophiles      | 1        |
| Myelocytes        | 0        |
| Juveniles         | 0        |
| Stab cells        | 1        |
| Segmented cells   | 69       |
| Lymphocytes       | 26       |
| Monocytes         | 2        |

He was readmitted on our service on April 30 with dyspnea, orthopnea, edema, nausea, vomiting, and distressing cough; B.P.  $\frac{180}{100}$ . Digitalis was withheld for six days and then commenced again. He improved considerably and was discharged on May 28.

His course was followed through the Out-patient Department and he was re-admitted on October 30 on account of incessant cough and decompensation; there was bloating of the abdomen, probably ascites, and edema of the legs. The liver was enlarged and tender. He had been receiving 25 drops of tincture of digitalis three times a day previous to admission. Because he had begun to vomit, it was considered that the patient was showing early symptoms of digitalis intoxication and the drug was stopped.

The laboratory findings at the time of this admission were of special interest.

|          |                                   |          |
|----------|-----------------------------------|----------|
| 10/30/30 | White blood count                 | 12,000   |
|          |                                   | PER CENT |
|          | Basophiles                        | 1        |
|          | Eosinophiles                      | 9        |
|          | Juveniles                         | 0        |
|          | Myelocytes                        | 0        |
|          | Stab cells                        | 3        |
|          | Segmented cells                   | 55       |
|          | Lymphocytes                       | 30       |
|          | Monocytes                         | 2        |
| 11/ 3/30 | Blood eosinophiles                | 26       |
| 11/ 7/30 | Blood eosinophiles                | 24       |
|          | Sputum contained no eosinophiles. |          |
|          | Stool contained no parasites.     |          |

The rapidly rising eosinophile count attracted much attention. An exhaustive search was made for parasitic infection but none could be found. A complement-fixation test for echinococcus was negative. There was no dermatitis or other obvious dermatological condition.

At this time, the literature concerning the relation between digitalis and eosinophilia came to our notice and it was decided to omit digitalis administration as long as possible in order to observe the effect on the differential blood count.

|          |                    |             |
|----------|--------------------|-------------|
| 11/13/30 | Blood eosinophiles | 20 per cent |
|----------|--------------------|-------------|

The patient, who had received no digitalis for two weeks, was beginning to show evidence of increasing decompensation.

|          |                    |             |
|----------|--------------------|-------------|
| 11/17/30 | Blood eosinophiles | 12 per cent |
|----------|--------------------|-------------|

Stool negative for parasites

|          |                    |             |
|----------|--------------------|-------------|
| 11/19/30 | Blood eosinophiles | 11 per cent |
|----------|--------------------|-------------|

Dr. L. W. Dean examined the patient at this time and made the following report on his nasal condition. "The nasal mucosa is reddened, the tint being a little darker than normal. The turbinates are of normal size. There is complete absence of the edema which usually characterizes the presence of eosinophiles in the nasal smear." Nasal smear, however, showed:

|                    |          |
|--------------------|----------|
|                    | PER CENT |
| Eosinophiles       | 55       |
| Lymphocytes        | 31       |
| Polymorphonuclears | 14       |

|          |   |             |  |
|----------|---|-------------|--|
| 11/20/30 | The patient was showing marked signs of decompensation and it was decided that digitalis therapy should be resumed. He received 8 cat units, or 0.8 gm., of digitalis leaf at 3 P.M. and 4 cat units, or 0.4 gm. more, at 10 P.M. |             |  |
| 11/21/30 | There was a marked improvement in symptoms and appearance.  |             |  |
|          | Blood eosinophiles  | 19 per cent |  |
| 11/23/30 | Receiving 0.1 gm. of powdered digitalis leaf per day he felt well.  |             |  |
|          |   | PER CENT    |  |
|          | Blood eosinophiles  | 30          |  |
| 11/25/30 | Blood eosinophiles  | 30          |  |
| 11/30/30 | White blood cells   | 9,750       |  |
|          |   | PER CENT    |  |
|          | Blood eosinophiles  | 30          |  |
| 12/ 3/30 | Blood eosinophiles  | 30          |  |
| 12/ 8/30 | Blood eosinophiles  | 30          |  |

Upon this maintenance dose of digitalis the eosinophilia was held at a constant level. The compensation of the heart seemed to be restored. The cough diminished. He was able to be up most of the time and although his capacity for exertion was greatly limited, he was discharged on Dec. 13, 1930, with directions to take 60 minims of a tincture of digitalis each day.

Decompensation of the heart began almost immediately after discharge from the hospital and he was readmitted on Dec. 29, 1930. He showed orthopnea, cyanosis, ascites, and edema. The heart sounds were of poor quality and the liver was much enlarged.

|                    |             |
|--------------------|-------------|
| Blood eosinophiles | 11 per cent |
|--------------------|-------------|

He never rallied after admission. He developed a temperature of 41.2° C., became irrational, stuporous, and finally died on Jan. 3, 1931.

At autopsy the heart showed sclerosis and scarring of the rheumatic type, causing stenosis of the mitral valve and insufficiency of the aortic valve. There was cardiac hypertrophy and chronic myocarditis. Edema of the lungs and chronic passive congestion of the liver, kidneys, and viscera were apparent. No parasites were found.

#### COMMENT

It is interesting that the patient had been under observation for a year and four months before eosinophilia was noted. Although digitalis had been given on more than one occasion, when the high eosinophile count was first discovered, he had been receiving outside of the hospital what appeared to be a mildly intoxicating dose. The history makes it apparent that no particular preparation of digitalis could be blamed for the eosinophile response which at one time followed a tincture given in the Out-patient Department and at another seemed to be induced by large doses of the powdered leaf.

The relationship of digitalis administration to eosinophilia during the later admissions is shown in Fig. 1.

At the time the blood count was showing a persistent eosinophilia of about 30 per cent (see next to last admission) the patient was sub-

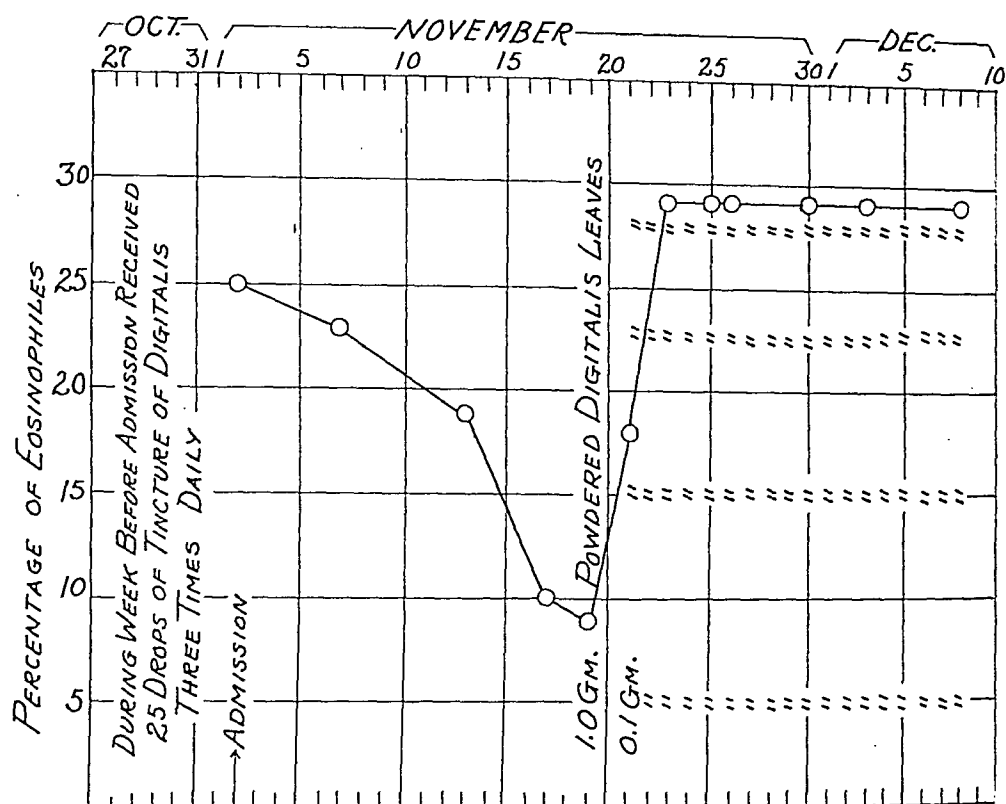


Fig. 1.—Relationship of eosinophilia to digitalis medication, showing apparent response both to tincture of digitalis given before admission and to powdered digitalis leaf administered in the hospital.

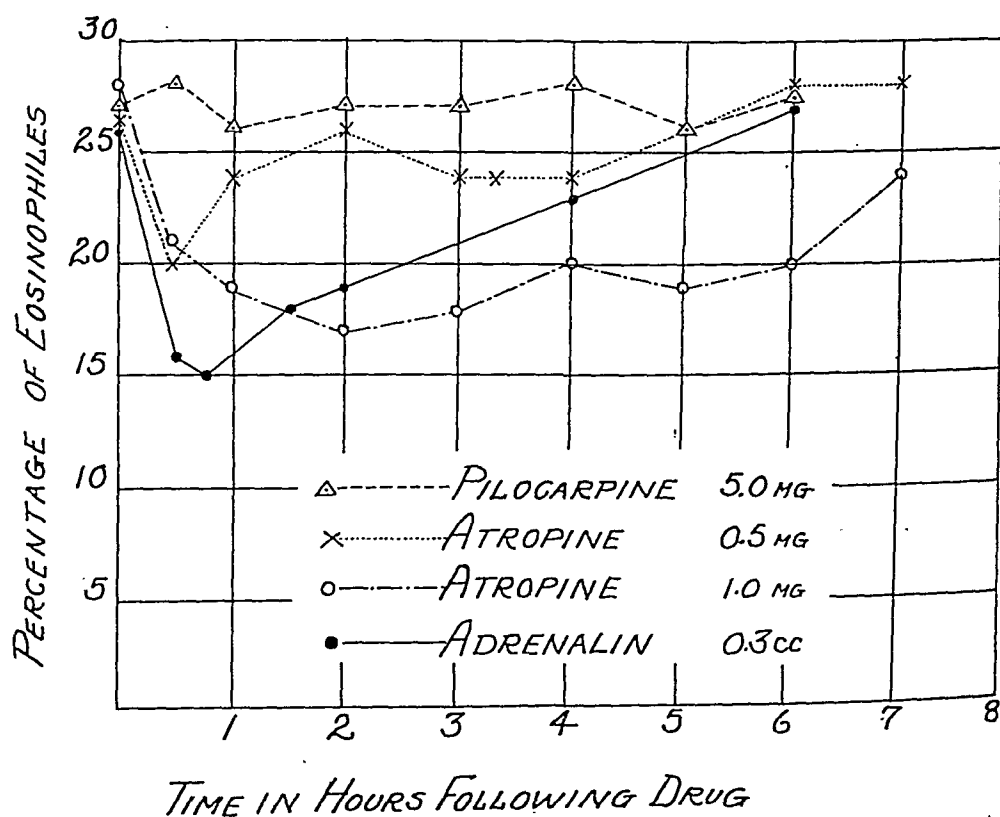


Fig. 2.—The effects of pilocarpine, atropine, and adrenalin on the eosinophile count.

jected to a series of experiments with atropine, adrenalin, and pilocarpine. Clinically, he showed no unusual susceptibility to any of these drugs. The effects on the eosinophile count are shown in Fig. 2.

Pilocarpine was without effect. Adrenalin produced a sharp drop with a gradual rise to the original level. Atropine, in a dose of 0.5 mg., caused a rapid though slight drop with almost immediate return. The effect of 1.0 mg. of atropine was more striking and much more persistent. In seven hours the eosinophilia had not returned to its original level.

Observations were made upon a series of 9 patients with heart disease, all of whom were under the full therapeutic effects of digitalis. In no case was there an eosinophilia of more than 4 per cent. The authors have had verbal reports, however, from Dr. J. F. Bredeek of 3 patients in whom an eosinophilia of 12 to 15 per cent could apparently be attributed to digitalis.

#### DISCUSSION

The eosinophilic response accompanying digitalis administration would appear to be of infrequent occurrence. It has attracted little attention and is not mentioned in textbooks of blood conditions. Its mechanism is by no means clear.

There is some evidence that the vagus or autonomic system has an influence on the number of eosinophile cells in the blood. A moderate eosinophilia is mentioned by Eppinger and Hess<sup>3</sup> as part of the syndrome of vagotonia. It is also described by Schilling.<sup>4</sup> Eosinophilia has been observed in association with tumors, especially in chest tumors involving the region of the vagus nerves. Hajos, Nemeth, and Enyedy<sup>5</sup> have shown that direct stimulation of the vagus produces an increase of eosinophiles in the blood of experimental animals. Bertellini and Falta<sup>6</sup> have caused an increase of eosinophiles in dogs and man upon administration of pilocarpine and a decrease after giving atropine.

The response of our patient to drugs partially confirms these observations. It is true that pilocarpine caused no change in the eosinophile count. Atropine, however, caused a diminished eosinophilia which after large doses tended to be persistent.

Because it is known that digitalis has an effect on the vagus center, it is somewhat tempting to assume that the eosinophilia is a result of vagal stimulation in a specially sensitive person. In our patient, however, it was not demonstrated that, clinically or from the standpoint of eosinophilic response, there was any unusual sensitiveness to the drugs which most affect the vagus.

#### SUMMARY

Eosinophilia apparently due to the administration of digitalis is reported. Similar cases in the literature are cited. Observations have

been made on the effect of adrenalin, atropine, and pilocarpine on the eosinophile count. Eosinophilia as an effect of vagus stimulation is briefly discussed. Studies of the blood of 9 other fully digitalized patients revealed no abnormal eosinophilia.

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# OBSERVATIONS ON THE DURATION OF THE ELECTRICAL SYSTOLE OF THE HEART, WITH SPECIAL REFERENCE TO THE EFFECT OF DIGITALIS\*

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THE significance of changes in the duration of the electrical systole is a problem which still remains to be solved. In the electrocardiogram, we consider as the duration of systole the time interval between the onset of the QRS wave and the end of the T-wave. While this Q-T interval may not exactly correspond to the actual systole of the heart, most authors agree that it is a satisfactory index of its duration and sufficiently accurate for comparative studies.

The first fact which attracts our attention when comparing different electrocardiographic tracings, is the effect of heart rate on the Q-T interval. In cases of bradycardia the Q-T interval is long, while in cases of tachycardia it is short. If we analyze a group of normal tracings, we make the further observation that, while systole shortens with increasing heart rate, diastole does so still more rapidly. For example, at a rate of 50 beats per minute, the Q-T interval will be approximately 0.40 second, the total cardiac cycle about 1.16 seconds; while at a rate of 135 per minute, the Q-T interval will be 0.29 second and the whole cardiac cycle only 0.44 second. In other words, at a rate of 50, systole occupies nearly one third of the cardiac cycle; while at a rate of 135, it fills more than two thirds of the cardiac cycle.

The P-R interval varies with the heart rate in the same manner.

The first one to study the duration of the electrical systole systematically, was Fridericia<sup>5</sup> (1920). From 50 carefully selected normal cases he published a table of normal values for the duration of the Q-T interval at heart rates varying from 50 to 135, and constructed a formula for the determination of the normal average duration of the Q-T interval, which he expresses as follows:

$$S = 8.22 \cdot \sqrt[3]{p}$$

(S = Q-T interval, p = pulse period.)

Fridericia's normal values were confirmed by Miki,<sup>10</sup> Pardee,<sup>17</sup> and P. D. White and S. G. Mudd.<sup>18</sup> Another formula suggested by Lombard and Cope,<sup>2, 16</sup> was proved less reliable by comparative studies of Miki.

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Besides the rate, another factor which has a definite effect upon the duration of the electrical systole is the administration of digitalis. The quantitative measurement of this effect is the object of the present study.

Twenty-one patients with definite cardiac disease, but with regular rhythm were selected. Patients with irregular heart action, especially those with auricular fibrillation, had to be excluded, for in those patients it is impossible to determine accurately the rate per minute from a tracing which shows only 8 to 12 ventricular complexes, and, therefore, it is also impossible to determine the normal value of Q-T for them. Measurements taken from the three different leads of the same patient varied up to 18 per cent, if the direction of T was the same in all of them, and varied still more, if T was inverted in one or two leads. Fridericia observed that with inversion of the T-wave the S-T interval

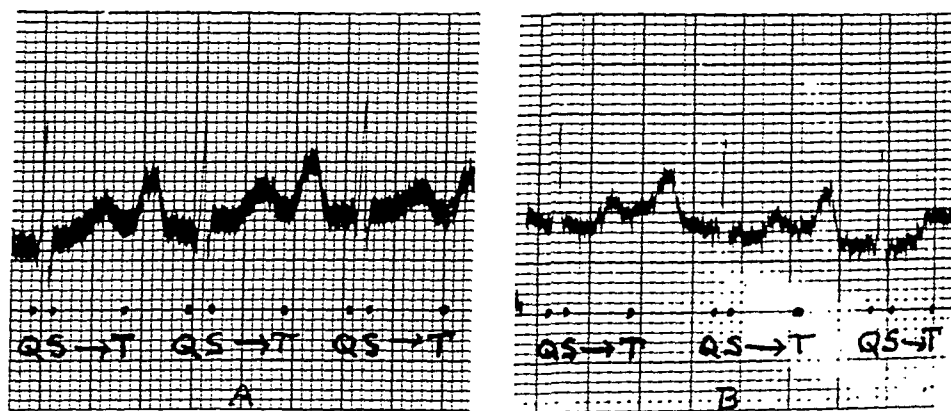


Fig. 1.—Case 10. A, before digitalization; B, after digitalization.

The QRS-T interval was measured first, from the beginning of Q to the end of S. Then the S-T interval was measured, from the end of S to the end of T. The Q-T interval was obtained by the addition of the QRS and the S-T intervals.

was always shorter than with an upright T. This finding is confirmed in the present study. All final measurements were done on Lead II.

The measurements were carried out as follows: The QRS interval was measured first, from the beginning of Q to the end of S. Then the S-T interval was measured, from the end of S to the end of T. These measurements were done on three different ventricular complexes and the average of the three values obtained was taken as the duration of QRS and S-T. The Q-T interval, the duration of the electrical systole, was obtained by the addition of the QRS and the S-T intervals. For all measurements in this series, the Cambridge Record Measuring Machine was used, a comparator designed after plans of Captain B. H. Elliott, R.A.

The Q-T interval was then compared with the normal established by Fridericia. The difference between the Q-T interval of each case and that normal was calculated for each case and expressed in per

cent. Whenever possible, three electrocardiograms were taken, one before digitalization, another immediately after digitalization, and a third after digitalis had been discontinued for some time. Usually, the patients received 2.8 gm. of powdered digitalis in one week. Fig. 1 shows the electrocardiograms (Lead II only) of a typical case before and after digitalization and illustrates the method of measuring the Q-T interval.

The effect of digitalis in the form of the electrocardiogram has been well known since the studies by Cohn, Fraser, and Jamieson,<sup>1</sup> in 1915. These authors described the characteristic changes of the T-wave, gradual depression and eventual inversion, which they saw appear from thirty-six to forty-eight hours after digitalis medication was begun, and which persisted from five to twenty-two days. But they did not concern themselves with the effect of the drug on the *duration* of the ventricular complex. That effect of digitalis on the Q-T interval is presented in Table I. This shows that shortening of the Q-T interval was demonstrable in all of 21 cases. The degree of shortening varied from 2 per cent to 41 per cent. In no case was a prolongation of the Q-T interval produced. The more prolonged the Q-T interval had been before digitalization, the more marked was the shortening. In Case 16, in which a 41 per cent decrease was observed, the Q-T interval had been 23 per cent above normal before digitalization. However, patients with an electrical systole of normal duration also showed definite shortening after digitalis.

It is important to note that the shortening always took place in the S-T portion of the ventricular complex. The duration of the QRS interval was not affected by digitalis in the same way as the S-T interval. Allowing for the effect of changes in rate, it was found that only in 10 out of 21 cases was the QRS interval shortened by digitalis; in 6 cases it was lengthened, and in 5 cases it remained unchanged.

Shortening of the Q-T interval was more marked when the rate previous to digitalization was comparatively slow. In that group, the greatest degree of original prolongation was found. The degree of shortening was not proportionate to the clinical digitalis effect. The greatest shortening of the Q-T interval was not accompanied by the greatest drop in heart rate, nor by the most marked relief of symptoms of cardiac failure. Also, the shortening was not proportionate to the amount of digitalis taken.

Because the effect of digitalis on the duration of the electrical systole is so constant, it is suggested that the phenomenon may be utilized for a clinical purpose, and that measurement of the Q-T interval may serve as a new method for estimating digitalis effect.

We have been accustomed to use other methods for the estimation of digitalis effect. We observe changes in rate and rhythm, altera-

TABLE I

| NO. | NAME  | NO. AND DATE OF ELECTRO-CARDI-GRAM | INTERPRETATION  | RAVE | QRS   | $\beta$ -T | Q-T   | NOR-MALE PULSATION OR Q-T | PRO-LONGA-TION | CLINICAL DIAGNOSIS  | MEDICATION   | MISCEL-LEANEOUS                            |
|-----|-------|------------------------------------|---|------|-------|------------|-------|---------------------------|----------------|---|--|--|
| 1   | T. S. | 16620<br>8/9/29                    | Right ventricular prepon-derance.*  | 90   | 0.056 | 0.350      | 0.406 | 0.333                     | 22%            | Arteriosclerosis; car-<br>dine enlargement;<br>arterial hyperten-<br>sion; congestive<br>heart failure.   | No digitalis.                                      |  |
|     | T. S. | 16686<br>8/16/29                   | Left ventricular prepon-derance; notching of QRS; T-waves low; occasional ventricular premature beat.   | 76   | 0.084 | 0.290      | 0.374 | 0.353                     | 0%             |   | Thinct. digitalis, 450<br>minims since<br>8/11/29. |  |
| 2   | S. P. | 17001<br>9/10/29                   | Right ventricular prepon-derance; T <sub>a</sub> diphasic.  | 60   | 0.081 | 0.379      | 0.400 | 0.382                     | 20%            | Rheumatic mitral<br>stenosis, mitral in-<br>sufficiency, aortic<br>stenosis and insuf-<br>ficiency; cardiac<br>enlargement; con-<br>gestive heart fail-<br>ure. | No digitalis.                                      | Diagnosis<br>confirmed<br>by autop-<br>sy. |
|     | S. P. | 17069<br>9/26/29                   | Right ventricular prepon-derance; T <sub>2</sub> and T <sub>3</sub> in-verted; T <sub>2</sub> and T <sub>3</sub> prominent; P <sub>1</sub> di-<br>phasic. | 96   | 0.080 | 0.233      | 0.313 | 0.326                     | 4%             |   | Thinct. digitalis, 400<br>minims since<br>9/10/29. |  |
| 3   | A. B. | 17126<br>10/2/29                   | Left ventricular prepon-derance; T <sub>1</sub> inverted.   | 78   | 0.087 | 0.358      | 0.445 | 0.350                     | 27%            | Arteriosclerosis; car-<br>dine enlargement;<br>arterial hyperten-<br>sion.  | No digitalis.                                      | Cor bovinum<br>(x-rays)                    |
|     | A. B. | 17206<br>10/9/29                   | Left ventricular prepon-derance; T <sub>1</sub> inverted;<br>R-T transition abnor-<br>mal.  | 68   | 0.085 | 0.268      | 0.353 | 0.366                     | 4%             |   | Pulv. digitalis, 2.6<br>gm. since 10/2/29.         |  |
|     | A. B. | 17277<br>10/16/29                  | Left ventricular prepon-derance; T <sub>1</sub> and T <sub>2</sub> in-<br>verted.   | 78   | 0.082 | 0.303      | 0.385 | 0.350                     | 10%            |   | No digitalis since<br>10/9/29.                     |  |
|     | A. B. | 18287<br>1/8/30                    | Left ventricular prepon-derance; T <sub>1</sub> inverted;<br>T <sub>2</sub> partially inverted.   | 84   | 0.104 | 0.322      | 0.426 | 0.340                     | 25%            |   |  |  |

\*Where the term "right ventricular preponderance" is used, the ventricular complex is inverted in Lead I, upright in Lead III.

TABLE I—CONT'D

| 4 | R. L. | 17205<br>10/9/29  | Slight left ventricular<br>preponderance.   | 98  | 0.067 | 0.275 | 0.342 | 0.324 | 6%   | Rheumatic mitral<br>stenosis and insuf-<br>ficiency; transient<br>hypertension                                  | No digitalis.<br>Pulv. digitalis, 1.9<br>gm. 10/9/29.<br>10/13/29. | Digitalis<br>stopped<br>because of<br>nausea.               |
|---|-------|-------------------|---|-----|-------|-------|-------|-------|------|---|--|---|
|   |       |                   |   |     |       |       |       |       |      |   |  |   |
|   | R. L. | 17279<br>10/16/29 | Slight left ventricular<br>preponderance; T <sub>1</sub> and<br>T <sub>2</sub> lower; T <sub>2</sub> semi-in-<br>verted.  | 125 | 0.063 | 0.211 | 0.274 | 0.299 | — 8% |   |  |   |
|   | R. L. | 17854<br>12/4/29  | Left ventricular prepon-<br>derance.  | 104 | 0.060 | 0.269 | 0.329 | 0.317 | 4%   |   | No digitalis since<br>10/13/29.                                    |   |
| 5 | Y. A. | 17657<br>11/14/29 | Left ventricular prepon-<br>derance; T <sub>2</sub> inverted.   | 73  | 0.066 | 0.317 | 0.383 | 0.358 | 7%   | Lactic aortic insuf-<br>ficiency and<br>stenosis.   | No digitalis.  |   |
|   | Y. A. | 17702<br>11/21/29 | Left ventricular prepon-<br>derance; T <sub>2</sub> inverted.   | 60  | 0.069 | 0.316 | 0.385 | 0.382 | 1%   |   | Tinct. digitalis, 210<br>minims 11/15/29.<br>11/17/29.             |   |
| 6 | S. S. | 17620<br>11/13/29 | Left ventricular prepon-<br>derance; QRS notched<br>in all leads; P <sub>1</sub> and T <sub>1</sub><br>slightly inverted. | 85  | 0.115 | 0.272 | 0.387 | 0.339 | 14%  | Arteriosclerosis; cor-<br>onary arterioscler-<br>osis; arterial hyper-<br>tension; congestive<br>heart failure. | No digitalis.  | Marked di-<br>latation<br>of left<br>ventricle<br>(x-rays). |
|   | S. S. | 17727<br>11/21/29 | Left ventricular prepon-<br>derance; QRS notched<br>in all leads; T <sub>1</sub> semi-<br>inverted.                       | 78  | 0.103 | 0.281 | 0.384 | 0.350 | 9%   |   | Tinct. digitalis, 180<br>minims since<br>11/14/29.                 |   |
| 7 | S. F. | 17722<br>11/21/29 | Tendency to left ventric-<br>ular preponderance; P <sub>2</sub><br>slightly inverted.                                     | 107 | 0.072 | 0.274 | 0.346 | 0.314 | 10%  | Rheumatic mitral<br>stenosis  | No digitalis.  |   |
|   | S. F. | 17782<br>11/27/29 | Tendency to left ventric-<br>ular preponderance;<br>all T-waves flatter.  | 96  | 0.065 | 0.273 | 0.338 | 0.326 | 4%   |   | Pulv. digitalis, 2.4<br>gm. since 11/21/29.                        |   |
| 8 | G. G. | 17552<br>11/7/29  | Left ventricular prepon-<br>derance.  | 80  | 0.058 | 0.290 | 0.348 | 0.316 | 1%   | Coronary arterioscler-<br>osis  | None.  |   |
|   | G. G. | 17634<br>11/14/29 | Left ventricular prepon-<br>derance; one extra-<br>systole of auricular or-<br>igin recorded.                             | 81  | 0.050 | 0.253 | 0.303 | 0.344 | ~13% |   | Pulv. digitalis, 2.8 gm.<br>since 11/7/29.                         |   |
|   | G. G. | 17781<br>11/27/29 | Left ventricular prepon-<br>derance; R-T transi-<br>tion abnormal in<br>Leads I and II                                    | 84  | 0.049 | 0.298 | 0.347 | 0.310 | 2%   |   | None since 11/14/29.   |   |

TABLE I—CONT'D

| NO. | NAME   | NO. AND DATE OF ELECTRO-CARDIO-GRAM | INTERPRETATION  | RATE | QRS   | S-T   | Q-T   | NORMAL DURATION OF Q-T | PRO-LONGATION | CLINICAL DIAGNOSIS  | MEDICATION                                  | MISCELLANEOUS         |
|-----|--------|-------------------------------------|---|------|-------|-------|-------|------------------------|---------------|---|---|-----------------------|
| 9   | A. IL. | 17695<br>11/20/29                   | T <sub>2</sub> inverted.  | 91   | 0.074 | 0.282 | 0.356 | 0.331                  | 8%            | Transient hypertension  | None.                                       |                       |
|     | A. IL. | 17783<br>11/27/29                   | Inversion of T and abnormal R-T transition in all leads.  | 70   | 0.074 | 0.263 | 0.337 | 0.362                  | 7%            |   | Pulv. digitalis, 2.8 gm. since 11/20/29.    |                       |
|     | A. IL. | 17956<br>12/12/29                   | T <sub>2</sub> slightly inverted.   | 90   | 0.065 | 0.247 | 0.312 | 0.333                  | 6%            |   | None since 11/27/29.                        |                       |
|     | A. IL. | 18455<br>1/2/30                     | T <sub>2</sub> slightly inverted.   | 80   | 0.079 | 0.253 | 0.332 | 0.346                  | 4%            |   |   |                       |
|     | E. D.  | 16311<br>7/2/29                     | Right ventricular preponderance; T <sub>2</sub> and T <sub>3</sub> large; P-R, 0.28 sec.  | 96   | 0.077 | 0.293 | 0.370 | 0.326                  | 13%           | Rheumatic mitral stenosis and tricuspid insufficiency;            | None.                                       |                       |
|     | E. D.  | 17927<br>10/10/29                   | Tendency to right ventricular preponderance; P prominent and broad in all leads; P-R, 0.28 sec.   | 92   | 0.077 | 0.276 | 0.353 | 0.331                  | 7%            | Cardiac enlargement; congestive heart failure.                    | None.                                       |                       |
|     | E. D.  | 18118<br>12/26/29                   | Right ventricular preponderance; T <sub>2</sub> inverted; P <sub>1</sub> notched; P <sub>2</sub> and P <sub>3</sub> prominent; P-R, 0.34 sec. | 90   | 0.067 | 0.240 | 0.307 | 0.333                  | 8%            |   | Pulv. digitalis, 3.0 gm. 12/18/29-12/26/29. |                       |
|     | I. P.  | 18561<br>1/30/30                    | Left ventricular preponderance; T <sub>1</sub> slightly inverted.   | 87   | 0.069 | 0.239 | 0.308 | 0.337                  | 9%            | Arteriosclerosis; cardiac enlargement; coronary arteriosclerosis  | None.                                       | Ceased Jan. 10, 1931. |
|     | I. P.  | 18705<br>2/13/30                    | Left ventricular preponderance; T <sub>1</sub> inverted; T <sub>2</sub> lower than before.  | 81   | 0.061 | 0.228 | 0.289 | 0.345                  | 16%           |   | Pulv. digitalis, 2.8 gm. since 1/30/30.     |                       |
|     | N. K.  | 18854<br>2/26/30                    | Left ventricular preponderance.   | 89   | 0.080 | 0.320 | 0.400 | 0.334                  | 20%           | Arteriosclerosis; cardiac enlargement; coronary arteriosclerosis. | None.                                       |                       |
| 12  | N. K.  | 18954<br>3/5/30                     | Left ventricular preponderance; T <sub>2</sub> slightly inverted.   | 77   | 0.093 | 0.266 | 0.359 | 0.351                  | 2%            |   | Pulv. digitalis, 3.0 gm. since 2/26/30.     |                       |

TABLE I—CONT'D

| 13 | I. K. | 18867<br>2/27/30  | No abnormalities.  | 78  | 0.077 | 0.314 | 0.391 | 0.350 | 12%  | Arteriosclerosis; cardiac enlargement; arterial hypertension; congestive heart failure.                                     | None.  | Pulv. digitalis, 2.8 gm. since 2/27/30. | Diagnosis confirmed by autopsy. |
|----|-------|-------------------|--|-----|-------|-------|-------|-------|------|---|--|---|---------------------------------|
|    |       |                   |  |     |       |       |       |       |      |   |  |   |                                 |
|    | I. K. | 18967<br>3/ 6/30  | Left ventricular preponderance; T <sub>3</sub> inverted.   | 100 | 0.075 | 0.268 | 0.343 | 0.321 | 7%   |   |  |   |                                 |
| 14 | O. H. | 16913<br>9/10/29  | Left ventricular preponderance; T <sub>1</sub> slightly inverted; R-T transition slightly above baseline in Leads II and III.                  | 102 | 0.093 | 0.206 | 0.299 | 0.320 | 7%   | Luetic aortic stenosis and insufficiency; coronary arteriosclerosis; cardiac enlargement; congestive heart failure.         | None.  |   |                                 |
|    | O. H. | 17429<br>10/29/29 | Left ventricular preponderance; R-T transition abnormal in Leads I and III.  | 83  | 0.105 | 0.250 | 0.355 | 0.342 | 4%   |   | Tinct. digitalis, 300 minims.                |   |                                 |
| 15 | L. F. | 18770<br>2/18/30  | R <sub>3</sub> low; T <sub>3</sub> inverted.   | 90  | 0.075 | 0.234 | 0.309 | 0.333 | — 9% | Subacute bacterial endocarditis; mitral stenosis and insufficiency; aortic insufficiency; embolic focal glomerulonephritis. | None.  |   |                                 |
|    | L. F. | 18806<br>2/20/30  | T <sub>2</sub> and T <sub>3</sub> inverted.  | 89  | 0.085 | 0.208 | 0.293 | 0.334 | —12% |   | Tinct. digitalis, 120 minims.                |   |                                 |
|    | L. F. | 18949<br>3/ 5/30  | R <sub>3</sub> low; T-waves inverted in all leads; R-T transition abnormal in all leads; P <sub>2</sub> inverted.                              | 76  | 0.080 | 0.187 | 0.267 | 0.352 | —24% |   | Tinct. digitalis, 1170 minims.               |   |                                 |
| 16 | J. Z. | 18982<br>3/ 7/30  | T <sub>1</sub> inverted, cove-shaped; T <sub>2</sub> partially inverted; R <sub>3</sub> very low.  | 95  | 0.070 | 0.332 | 0.402 | 0.327 | 23%  | Luetic aortitis; aneurysm; aortic insufficiency; coronary thrombosis  | None.  |   |                                 |
|    | J. Z. | 19056<br>3/13/30  | P-R, 0.25 sec.; occasional blocked auricular beats.  | 126 | 0.074 | 0.168 | 0.242 | 0.298 | —18% |   | Tinct. digitalis, 1640 minims since 3/8/30.  |   |                                 |
| 17 | J. M. | 20119<br>6/28/30  | Left ventricular preponderance; T <sub>1</sub> semi-inverted; high voltage.  | 81  | 0.100 | 0.204 | 0.394 | 0.345 | 14%  | Rheumatic aortic insufficiency; congestive heart failure.   |  |   |                                 |
|    | J. M. | 20197<br>7/ 9/30  | Left ventricular preponderance; high voltage; T <sub>1</sub> and T <sub>2</sub> deeply inverted; nodal rhythm with P frequently following QRS. | 85  | 0.077 | 0.251 | 0.328 | 0.340 | — 4% |   | Tinct. digitalis, 240 minims 6/30/30-7/4/30. |   |                                 |

TABLE I—CONT'D

| NO. | NAME  | NO. AND DATE OF ELECTRO-CARDIO-GRAM | INTERPRETATION  | RATE | QRS   | S-T   | Q-T   | NOR-MAL DURA-TION OF Q-T | PRO-LON-GA-TION | CLINICAL DIAGNOSIS  | MEDICATION  | MISCEL-LANEOUS                   |
|-----|-------|-------------------------------------|---|------|-------|-------|-------|--------------------------|-----------------|---|---|----------------------------------|
| 18  | S. K. | 16004<br>6/1/29                     | Right ventricular prepon-derance.   | 100  | 0.113 | 0.244 | 0.357 | 0.321                    | 11%             | Rheumatic mitral stenosis and insuf-ficiency; aortic in-sufficiency.  | None.   | Diagnosis confirmed by autop-sy. |
|     | S. K. | 16277<br>6/28/29                    | Left ventricular prepon-derance.  | 61   | 0.078 | 0.269 | 0.347 | 0.380                    | 9%              |   | Tinct. digitalis, 795 minims since 6/1/29.                            |                                  |
| 19  | I. H. | 19699<br>5/12/30                    | T <sub>2</sub> and T <sub>3</sub> partially in-verted; P-R, 0.24 sec.                       | 89   | 0.083 | 0.210 | 0.293 | 0.334                    | 12%             | Rheumatic mitral stenosis; mitral in-sufficiency; aortic and tricuspid insuf-ficiency.                      | Pulv. digitalis, 5.4 gm. 4/14/30-5/7/30.                              | Diagnosis confirmed by autop-sy. |
|     | I. H. | 20249<br>7/17/30                    | T continuous with QRS; P-R, 0.32 sec.   | 100  | 0.076 | 0.179 | 0.255 | 0.321                    | 21%             |   | No digitalis 5/8/30-6/7/30; tinct. dig-italis, 70 c.c. since 6/24/30. |                                  |
| 20  | I. H. | 19673<br>5/9/30                     | QRS notched in all leads; P <sub>1</sub> and P <sub>2</sub> notched.                        | 78   | 0.079 | 0.312 | 0.391 | 0.350                    | 12%             | Subacute bacterial en-docarditis; patent ductus; mitral stenosis and insuf-ficiency; aortic in-sufficiency. | None.   | Diagnosis confirmed by autop-sy. |
|     | I. H. | 20042<br>6/17/30                    | Nodal rhythm; T <sub>2</sub> and T <sub>3</sub> inverted; R-T transition in Leads I and II. | 91   | 0.065 | 0.207 | 0.272 | 0.331                    | 18%             |   | Tinct. digitalis, 480 minims since 6/10/30.                           |                                  |
| 21  | J. P. | 21739<br>1/23/31                    | No abnormalities.   | 86   | 0.077 | 0.265 | 0.342 | 0.338                    | 1%              | Rheumatic mitral stenosis and insuf-ficiency; aortic in-sufficiency.  | None.   |                                  |
|     | J. P. | 21887<br>2/11/31                    | T <sub>2</sub> and T <sub>3</sub> partially in-verted.                                      | 94   | 0.067 | 0.248 | 0.315 | 0.329                    | 4%              |   | Pulv. digitalis, 2.1 gm. 1/24/31-1/31/31.                             |                                  |



tions in the form of the T-wave, and changes in conduction time. The results of the first two of these methods were compared with those of the new method which I propose. Such comparison yielded the following results: Slowing of the rate was in evidence in only 13 out of 21 cases (62 per cent). Changes in the form of the T-wave were found in 17 out of 21 cases (81 per cent). Shortening of the Q-T interval, on the other hand, was present in all of 21 cases (100 per cent). It thus seemed proved that shortening of the Q-T interval is the most reliable criterion of digitalis effect.

Slowing of the rate is an important clinical sign of digitalis effect. But it is not a reliable indicator. The rate is always subject to many accidental influences, such as temperature, emotions *et al.* That accounts for the fact that in our series only 13 out of 21 cases showed slowing, whereas 8 showed acceleration. The changes in the form of the T-wave are better indicators of digitalis effect. They appear early, two or three hours after the administration of a single dose of the tincture equal to one minim per pound of the patient's weight (Pardee). They appear before alterations in rhythm or conduction time are evident; and they are less subject to accidental influences. In our series, 17 out of 21 cases showed T-wave changes. Here the question arises why in 4 out of 21 cases no such T-wave changes could be detected. The answer may be that T-wave changes might be so minute as to escape observation. At any rate, the results of this method depend very much upon individual interpretation and can never be expressed by actual figures.

In the same 4 cases in which no changes in the form of the T-waves were in evidence, digitalis produced definite shortening of the electrical systole varying from 7 to 36 per cent. Consequently, shortening of the Q-T interval (always related to the respective heart rates) proved a better indicator of digitalis effect on the heart than the other methods. The new method appears reliable as long as the measurements obtained are taken not at their absolute values, but in their relation to the normal values established for the respective heart rates.

The first case of the series will illustrate this point. Here, the duration of systole was 0.406 sec. before digitalization, 22 per cent above normal. The heart rate was then 90 beats per minute. Digitalis shortened the duration of systole to 0.374 second, only 6 per cent above normal, while the heart rate came down to 76. There we can say that digitalis shortened the systole by 16 per cent. But it would be incorrect simply to subtract 374 from 406 and state that digitalis shortened the systole by 0.032 second. The results of the new method cannot be expressed in seconds, but only in percentage of the normal values. Still, one definite advantage of the method remains—the digitalis effect can be expressed by a single figure.

A study of the digitalis effect on the Q-T interval necessarily leads up to the larger problem: what significance have spontaneous changes in the duration of the electrical systole? What importance, in particular, has a prolongation of the Q-T interval? Fridericia<sup>9</sup> reported that abnormal prolongation of systole could be produced in healthy animal hearts by overburdening them suddenly, and that in man, an abnormal increase in the duration of systole was indicative of myocardial weakness. He mentions one case of mitral stenosis in which such prolongation was the forerunner of auricular fibrillation at a time when there were no other signs indicating poor prognosis. Another author, Miki,<sup>10</sup> found that after a series of extrasystoles the first normal contraction may be very short; and he concluded that damage to the heart muscle was indicated by shortening of systole rather than by lengthening it. When Miki discusses clinical cases, he does not state expressly that digitalis had not been administered. The same is true of most other workers. The author's investigation bears out the fact that shortening of the electrical systole must not be attributed to myocardial damage as long as digitalis effect is not ruled out. This consideration is of great importance, because in a group of patients with cardiac failure usually very few can be found who have not received digitalis.

Pardee<sup>17</sup> considers it "possible that the relation between heart rate and the duration of the ventricular complex may express the degree of cardiac dilatation at the various rates." White and Mudd<sup>18</sup> studied the problem in 50 normal and 163 abnormal persons and came to the conclusion that "the measurement of the duration of the Q-T interval of the electrocardiogram is apparently of little or no clinical value." One factor which these authors found exerting definite influence on the duration of the Q-T interval was the content of calcium in the blood serum. Only 5 such cases were studied by them. Two cases of tetany which showed marked diminution of the serum calcium both showed prolongation of the Q-T interval beyond the normal, with a return to normal as the blood calcium rose. This relationship had already been reported by Carter and Andrus.<sup>11</sup>

In my own investigation, I have thought it advisable to differentiate between two types of prolongation of the electrical systole: those with a QRS interval prolonged above the normal limit of 0.09 second, and those with a QRS interval of normal duration; viz., below 0.09 second. In the first group, prolongation of the electrical systole is due to abnormal conduction. Outstanding examples of this group are cases of bundle-branch block and most extrasystoles, especially of the ventricular variety. Here prolongation of the electrical systole is brought about chiefly by the widening of the QRS complexes. I was concerned, however, only with the second group where the QRS interval is of normal duration. In those cases prolongation of the electrical systole

is brought about by lengthening of the S-T interval. It is not the spreading of the contraction, but the contraction itself that is prolonged.

I have collected 54 such cases of normal rhythm with prolongation of the electrical systole. Only patients with a Q-T interval prolonged 10 per cent or more above Fridericia's normal were included in this group so as to rule out the influence of possible errors of measurement.\*

TABLE II

54 CASES WITH PROLONGATION OF THE Q-T INTERVAL  
(10 Per Cent or More Above Normal.)

|                                  |    |       |
|----------------------------------|----|-------|
| Arterial hypertension            | 24 | 44.4% |
| Rheumatic valvular heart disease | 14 | 25.9% |
| Thyroid diseases*                | 4  | 7.4%  |
| Subacute bacterial endocarditis  | 3  | 5.6%  |
| Coronary arteriosclerosis        | 2  | 3.7%  |
| Luetic aortic insufficiency      | 2  | 3.7%  |
| Cerebral arteriosclerosis        | 1  | 1.9%  |
| Cardiac neurosis                 | 1  | 1.9%  |
| Pneumonia, lobar                 | 1  | 1.9%  |
| Chronic pneumonitis              | 1  | 1.9%  |
| Pernicious anemia                | 1  | 1.9%  |
| Total                            | 54 | 100%  |

\*Two cases of substernal goiter with tracheal compression, two cases of Graves' disease.

All patients who had received either digitalis, which shortens systole, or quinidine, which prolongs it, were carefully excluded. Table II summarizes the diagnoses in this group. Forty-six of the 54 patients had definite evidence of heart disease; 24 out of the 54 had hypertension (44.4 per cent). The preponderance of arterial hypertension in this group is impressive. Fenn,<sup>12</sup> in 1922, had already found that clinical conditions accompanied by high blood pressure are often associated with prolongation of the Q-T interval. I observed that the higher degrees of prolongation occurred most frequently in hypertensive disease, and were not usually present in grave or fatal cases. Equally high values were obtained in rheumatic heart disease, although less frequently.

TABLE III

20 CASES WITH EXTREME PROLONGATION OF THE Q-T INTERVAL  
(20 Per Cent to 34 Per Cent Above Normal.)

|                                  |    |      |
|----------------------------------|----|------|
| Arterial hypertension            | 12 | 60%  |
| Rheumatic valvular heart disease | 4  | 20%  |
| Subacute bacterial endocarditis  | 1  | 5%   |
| Luetic aortic insufficiency      | 1  | 5%   |
| Graves' disease                  | 1  | 5%   |
| Chronic pneumonitis, right lung  | 1  | 5%   |
| Total                            | 20 | 100% |

\*The measurements in the previous series in which the effect of digitalis was studied were done twice, first without a comparator, and then again with the comparator. The results by the two methods differed so very little that it was not considered necessary to use the comparator for this and the following series.

From this group of 54 patients, there were then selected 20 patients with extreme prolongation of the electrical systole. Only those with a Q-T interval of 20 per cent or more above normal were included in this special group, which is summarized in Table III. Here 12 patients (60 per cent) had arterial hypertension as compared to 46 per cent in the larger group. All patients, except two, had very large hearts as demonstrated either by x-ray or by autopsy. Very often extreme dilatation was noted. It is certain, however, that prolongation of the electrical systole is a complex phenomenon and does not express cardiac dilatation alone. Two cases of marked dilatation were found with shortening of the electrical systole. Digitalis, which usually reduces the size of the heart but little, could not shorten the Q-T interval up to 41 per cent, if prolongation expressed dilatation only. Miki produced prolongation of the electrical systole experimentally in dogs by compressing the aorta. This experiment allows the same conclusion as does the prevalence of arterial hypertension in my group of clinical cases with prolonged Q-T interval; namely, that increased resistance to the systolic contraction of the heart is a principal factor in producing prolongation of the electrical systole.

Prolongation was found to be more frequently associated with bradycardia than with tachycardia. It would seem that with a heart rate of 60, a prolongation of 10 per cent may be of less significance than the same finding at a rate of 120. The highest degree of prolongation that I observed was 34 per cent (3 cases). It was noticed that the greatest prolongation was invariably found in those patients who showed no signs of cardiac failure. This observation, which agrees with earlier findings reported by Feil and Katz,<sup>13, 14, 15</sup> does not corroborate Fridericia's statement that prolongation of the electrical systole indicated myocardial weakness and poor prognosis. Rather it points toward the opposite conclusion.

TABLE IV  
Q-T INTERVAL IN 14 FATAL CASES OF AORTIC INSUFFICIENCY

| CASE NO. | DURATION OF R-T INTERVAL |                              |
|----------|--------------------------|------------------------------|
| 20339    | 30% prolongation         | marked prolongation: 4 cases |
| 20612    | 20% prolongation         |                              |
| 19406    | 28% prolongation         |                              |
| 15254    | 23% prolongation         |                              |
| 20119    | 7% prolongation          |                              |
| 18097    | 4% prolongation          | normal duration: 8 cases     |
| 20476    | normal duration          |                              |
| 16004    | normal duration          |                              |
| 18770    | normal duration          |                              |
| 18097    | normal duration          |                              |
| 16913    | normal duration          | marked shortening: 2 cases   |
| 18144    | 3% shortening            |                              |
| 18126    | 12% shortening           |                              |
| 19024    | 15% shortening           |                              |
| Total    | 14 cases                 |                              |

In seeking further for a possible prognostic significance of prolongation of the Q-T interval I collected a third group of cases (Table IV) made up of 14 patients with aortic insufficiency, mostly combined with other valvular lesions, who died during their hospital residence in 1930. Aortic insufficiency was selected because of its common association with extreme enlargement of the heart. Autopsies were performed on all 14 patients. Digitalized patients were carefully excluded. Only 4 of the 14 patients (29 per cent) showed marked prolongation of the electrical systole; 2 (14 per cent) showed marked shortening, and 8 (57 per cent) a normal duration of the Q-T interval. No definite prognostic significance can, therefore, be attached to either prolongation or shortening in this group.

#### SUMMARY

Twenty-one patients with definite cardiac disease, but with regular rhythm were selected and the effect of digitalis on the duration of the Q-T interval, the electrical systole of the heart, was studied. It was found that digitalis shortened the electrical systole up to 41 per cent in all of 21 cases. The shortening always took place in the S-T interval, while the QRS interval was neither definitely prolonged nor shortened. It is suggested that measurement of the Q-T interval may serve as a new method for estimating digitalis effect on the heart. This method was found more reliable than the older ones. Besides, it has the special advantage that it allows the digitalis effect to be expressed by a single figure.

In an effort to determine the significance of spontaneous changes in the duration of the electrical systole, especially of prolongation, 54 patients with normal rhythm and a Q-T interval prolonged 10 per cent or more above normal were collected. Twenty-four (44.4 per cent) of these 54 patients had arterial hypertension. In a narrower group of 20 patients with a Q-T interval prolonged 20 per cent or more above normal, a still higher proportion, 12 (60 per cent) had arterial hypertension. Prolongation of the electrical systole is usually associated with cardiac enlargement. That it does not indicate poor prognosis was borne out by the results in a third series, consisting of 14 fatal cases of aortic insufficiency. Only 4 (29 per cent) of these 14 cases showed marked prolongation of the Q-T interval.

I wish to express my appreciation to Dr. Marcus A. Rothschild and Dr. Irving R. Roth for their helpful suggestions.

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## THE ACCURACY OF EINTHOVEN'S EQUATION\*

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IN HIS earliest articles on the electrocardiogram, Einthoven<sup>1,2</sup> pointed out that the three standard leads adopted by him are related in such a way that any one of them may be calculated when the other two are known. He expressed this relation in the equation:

$$\text{Lead II} - \text{Lead I} = \text{Lead III}$$

which states that the deflection in Lead II is equal to the sum of the deflections in the other two leads.

This equation has frequently led to misunderstanding. Only recently an article has been published<sup>3</sup> in which the statement is made that it can only be exact when the triangle formed by the three leads is strictly equilateral. Actually, the equation is based upon the simple principle that a direct measurement of the potential difference between two points will give the same result as an indirect measurement in which the potential of each point is compared with that of a third point. If the potential of the right arm is represented by  $V_R$ ; the potential of the left arm, by  $V_L$ ; and the potential of the left leg, by  $V_F$ ; then, Lead I must be represented by  $V_L - V_R$ ; Lead II, by  $V_F - V_R$ ; and Lead III, by  $V_F - V_L$ . It is obvious that

$$(V_F - V_R) - (V_L - V_R) = (V_F - V_L) \quad (1)$$

and consequently that Einthoven's equation must hold equally well for any kind of a triangle whatsoever.

Einthoven, Fahr, and de Waart<sup>4</sup> pointed out that this equation does, however, involve the assumption that the current which flows through the galvanometer has no influence upon the potentials of the extremities connected to its terminals. They state that the effect mentioned must be too small to introduce a material error because the resistance of the galvanometer and the body is very large in comparison with the resistance of the heart muscle.

In a subsequent article by Einthoven, Bergansius, and Bijtel<sup>5</sup> however, it is shown that the accuracy of the formula does not depend upon the resistance of the galvanometer nor upon the assumption mentioned. It is demonstrated that, contrary to an opinion still very widely held, the method of standardizing the electrocardiogram is such

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that the potential differences measured are those that would have existed had the galvanometer not been connected to the body.

Inasmuch as the proof of this important principle given by Einthoven and his associates is so brief that it is rather hard to follow and has been generally overlooked, we repeat it here in a somewhat modified form.

In Fig. 1 the electromotive force generated by the heart at any instant is represented by  $E_1$ . The right and left arms, or any two points of the body surface, are represented by  $R$  and  $L$ , respectively. Be-

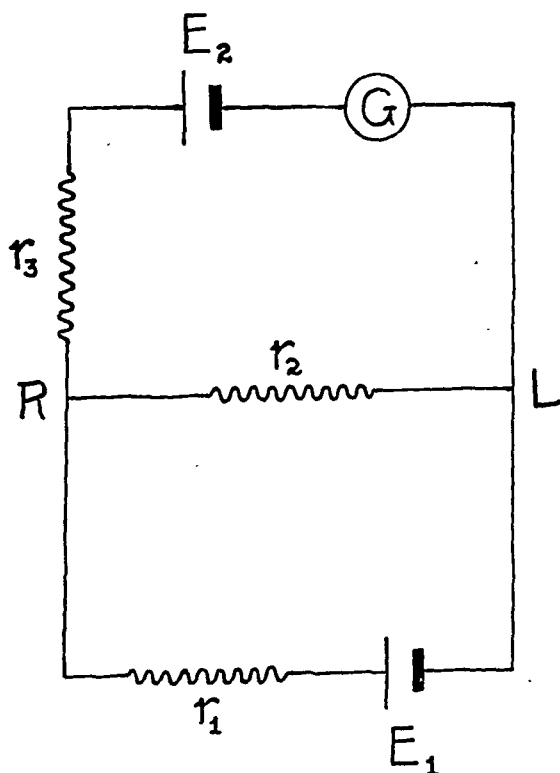


Fig. 1.

fore the attachment of the galvanometer terminals at these points the current  $I_1$  flowing through the body circuit, which contains the resistances  $r_1$  and  $r_2$ , is defined by the equation

$$I_1 = \frac{E_1}{r_1 + r_2} \quad (2)$$

and the potential difference between  $R$  and  $L$  by the expression

$$V_L - V_R = \frac{E_1 r_2}{r_1 + r_2} \quad (3)$$

When the galvanometer circuit containing the resistance  $r_3$ , but no electromotive force, is added by connecting the galvanometer termi-



nals at  $R$  and  $L$ , the current  $I_2$  flowing through the main circuit; that is, through the resistance  $r_1$ , will be represented by

$$I_2 = \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}} \quad (4)$$

and the current  $I_3$  through the galvanometer,  $G$ , by

$$I_3 = \frac{r_2}{r_2 + r_3} \times \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}} \quad (5)$$

The potential difference between  $R$  and  $L$  will obviously decrease somewhat when the galvanometer is attached.

If, at some point in diastole when the electromotive force  $E_1$ , generated by the heart is no longer acting, an electromotive force,  $E_2$  is introduced into the galvanometer circuit, the current  $I_4$  flowing through the galvanometer will be defined by the equation

$$I_4 = \frac{E_2}{r_3 + \frac{r_1 r_2}{r_1 + r_2}} \quad (6)$$

If the value of  $E_2$  is so adjusted that the deflection of the galvanometer in response to this electromotive force is equal to the deflection previously produced by the electromotive force generated by the heart; that is to say, so that  $I_4$  equals  $I_3$ , then

$$\frac{E_2}{r_3 + \frac{r_1 r_2}{r_1 + r_2}} = \frac{r_2}{r_2 + r_3} \times \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}} \quad (7)$$

or

$$E_2 = \frac{E_1 r_2}{r_1 + r_2} = V_L - V_R \quad (8)$$

Consequently,  $E_2$  is equal to the potential difference between  $R$  and  $L$  that would have been produced by  $E_1$ , if the galvanometer had not been connected to the body circuit. In this demonstration it is assumed that the method employed to introduce the standardizing electromotive force  $E_2$  does not alter the resistance of the galvanometer circuit. The accuracy of Einthoven's equation depends upon this requirement but upon no other condition. It is of course essential that

the electrodes used shall not polarize appreciably and that the skin be properly prepared so that it shall not introduce a leaky condenser into the circuit.

#### SUMMARY

The accuracy of Einthoven's equation does not depend upon the resistance of the string galvanometer. In a properly standardized electrocardiogram the deflection at any instant is an accurate measure of the potential difference that would have existed between the body points to which the galvanometer terminals were attached had the galvanometer not been connected with the body.

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## THE POTENTIAL VARIATIONS PRODUCED BY THE HEART BEAT AT THE APICES OF EINTHOVEN'S TRIANGLE\*

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THE electrocardiogram is a record of the time course of the difference in potential produced by the heart beat between the two points or regions of the body upon which the galvanometer electrodes rest. It may therefore be regarded as a combination of two curves, each of which represents the potential variations during the cardiac cycle beneath a single electrode. In the case of the records obtained from isolated strips of cardiac or skeletal muscle suspended in moist air, it is possible to determine the form of these constituent or unipolar curves, at least approximately, by killing the tissue beneath one electrode. Experiments of this kind have, however, no direct bearing upon the analysis of the clinical electrocardiogram. When the irritable tissue is surrounded by a large body of conducting medium, or when indirect leads are employed, it is not possible to prevent variations in the potential of one electrode by killing the tissue with which it is in contact.

For certain purposes it is desirable to know the form of the constituent curves of which the electrocardiogram is a combination, and we wish to describe a method of determining the potential variations produced by the heart beat at any point of the body. This method is based upon the principles set forth in a recent article from this laboratory.<sup>1</sup> It was there shown that Einthoven's equilateral triangle is based upon the laws which govern the distribution of electric currents in volume conductors. It will be recalled that Einthoven assumed that the resultant electromotive force produced by the heart at any instant may be represented by a "bipole"; that is to say, a positive and negative pole of equal strength very close together; located at the center of the triangle. The axis of this bipole, or doublet, was represented by an arrow pointing from the negative toward the positive pole; this axis is usually spoken of as the electrical axis of the heart. It was also shown, in the article referred to, that the potential  $V$  of any apex of the triangle is proportional to the cosine of the angle  $\theta$  made by the electrical axis with the line drawn from the center of

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the triangle to the apex in question. Referring to Fig. 1 we may define the potentials of the three apices of the triangle as follows:

$$V_R = A \cos \theta_1 \quad (1a)$$

$$V_L = A \cos \theta_2 \quad (1b)$$

$$V_F = A \cos \theta_3 \quad (1c)$$

In these equations  $A$  is merely a proportionality factor. We need not discuss here the factors upon which its value depends since all of these remain constant under the circumstances with which we are concerned.

Einthoven represented the deflections in the three standard leads by  $e_1$ ,  $e_2$ , and  $e_3$ , respectively, and expressed them in terms of the angle  $\alpha$  (Fig. 1) and  $E$ , the manifest potential difference. If we equate the

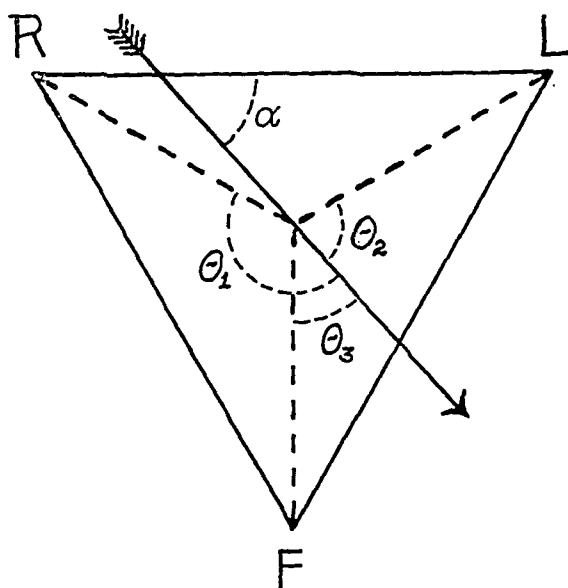


Fig. 1.

values of  $e_1$ ,  $e_2$ , and  $e_3$ , given by him to those derived from the equations given above we have

$$e_1 = V_L - V_R = E \cos \alpha = A (\cos \theta_2 - \cos \theta_1) \quad (2a)$$

$$e_2 = V_F - V_R = E \cos (\alpha - 60^\circ) = A (\cos \theta_3 - \cos \theta_1) \quad (2b)$$

$$e_3 = V_F - V_L = E \cos (120^\circ - \alpha) = A (\cos \theta_3 - \cos \theta_2) \quad (2c)$$

The angles  $\theta_1$ ,  $\theta_2$ , and  $\theta_3$  may, however, be expressed in terms of  $\alpha$ ; viz.,  $\theta_1 = 210^\circ - \alpha$ ;  $\theta_2 = \alpha + 30^\circ$ ;  $\theta_3 = 90^\circ - \alpha$ . By substituting these values in the first of the equations (2a) just given, we obtain

$$\begin{aligned} e_1 &= E \cos \alpha = A [\cos (30^\circ + \alpha) - \cos (210^\circ - \alpha)] \\ &= A (\sqrt{3} \cos \alpha) \end{aligned} \quad (3)$$

Consequently,

$$\begin{aligned} E &= \sqrt{3} A \\ V_F &= \frac{E}{\sqrt{3}} \cos (90^\circ - \alpha) = \frac{E}{\sqrt{3}} \sin \alpha. \end{aligned} \quad (4)$$

We now have an expression for the potential of the left leg in terms of  $E$  and  $\alpha$ . We may obtain a more convenient expression in the following way:

$$\begin{aligned} e_2 + e_3 &= E [\cos (\alpha - 60^\circ) + \cos (120^\circ - \alpha)] \\ &= E (\sqrt{3} \sin \alpha). \end{aligned} \quad (5)$$

Consequently,

$$V_F = \frac{e_2 + e_3}{3} = \frac{E}{\sqrt{3}} \sin \alpha. \quad (6a)$$

In the same way it may be shown that

$$V_R = - \frac{e_1 + e_2}{3} \quad (6b)$$

$$V_L = \frac{e_1 - e_3}{3} \quad (6c)$$

These expressions give the potentials of the three extremities, or the three apices of Einthoven's triangle, in terms of the deflections in the three leads. They therefore enable us to determine the potential at any point of the body at any instant with reference to the potential of this point at a time when the heart is producing no electric currents, a potential which we may for our purposes regard as zero. In other words, we can determine the potential variations produced by the heart beat at any body point. To do so we need merely to place the right-hand electrode of the galvanometer at this point and the left-hand electrode upon one of the extremities. The resulting record will give the difference in potential between the point under investigation and the extremity employed. The potential of the former is then computed by subtracting from the recorded curve the potential variations of the latter determined by formula from the appropriate standard leads. In order to carry out this procedure properly, two galvanometers are required. First of all, the three standard leads are recorded, taking two leads simultaneously so that synchronous points may be identified. The right-hand electrode of one galvanometer is then placed in contact with the point under investigation and the left-hand electrode upon the left leg. A record is then made, the second galvanometer being employed to inscribe Lead I simultaneously.

We may represent the potential of the point chosen by  $V_P$  and the deflection at any instant in the lead from this point to the left leg by  $e_4$ . We then have

$$V_F - V_P = e_4 \quad (7)$$

$$- V_P = e_4 - \frac{e_2 + e_3}{3} \quad (8)$$

In order to avoid confusion some explanation of the plus and minus signs in these and preceding equations is necessary. It has become conventional to take electrocardiograms in such a way that relative

negativity of the electrode attached to the right hand in Leads I and II produces an upward deflection in the completed record. Since an upward deflection is considered positive in measuring the electrocardiogram, it is necessary to represent Lead I by  $V_L - V_R = e_1$  in order to indicate that  $e_1$  becomes more positive as the right arm becomes more negative or the left arm more positive. In other words, the derivative of  $e_1$ , with respect to  $V_R$  must be negative and its derivative with respect to  $V_L$ , positive. The signs in the corresponding formulas for the other standard leads are determined in the same way. It has also become conventional in leading from points on or near the heart to points at a distance to use the right-hand electrode as the exploring electrode, so that an upward deflection indicates relative negativity of the point under investigation. For this reason negative values of  $V_P$  in equation (8) are plotted above the base line and positive values below. In plotting  $V_F$ , the potential of the left leg, which is ordinarily attached to the left-hand electrode in taking both standard and special leads, positive values are plotted above the base line and negative values below, because variations in the potential of the left-hand electrode have an effect upon the electrocardiogram opposite in sign to that produced by variations in the potential of the right-hand electrode.

In the article from this laboratory to which we have already referred it was pointed out that when one electrode is placed very close to the heart or upon its surface, the position of the second electrode, so long as it is distant from the heart, is of very little importance. The reason lies in the character of the laws which govern the distribution of electric currents in volume conductors. The magnitude of the effect exerted by the position of the distant electrode may now be accurately determined. Suppose that the right-hand electrode is placed upon the exposed ventricular surface and the left-hand electrode upon the left leg. In such direct leads the galvanometer may be employed at one-twentieth of its normal sensitivity. In order to free a curve obtained in this way from the influence exerted by potential variations at the leg electrode, it is only necessary to subtract from each ordinate  $\frac{e_2 + e_3}{60}$  millimeters, where

$e_2$  and  $e_3$  represent the deflections in Leads II and III, respectively, at the corresponding instant in the cardiac cycle. It is obvious that curves of this kind are, for all practical purposes, records of the potential variations of the exploring electrode alone.

In precordial leads, in which the exploring electrode is placed upon the precordium and the indifferent electrode upon the left leg, the galvanometer is ordinarily employed in this laboratory at one-half its normal sensitivity. To free curves obtained in this way from the influence exerted by potential variations at the distant electrode it is necessary, therefore, to subtract from each ordinate  $\frac{e_2 + e_3}{6}$  millimeters.

The potential variations of the leg electrode have a much greater influence upon the form of these curves than upon those obtained by direct leads of the kind mentioned. It is hoped that a method of estimating the magnitude of this influence and of eliminating it when desirable will be of service in their interpretation.

#### SUMMARY

A method is described by means of which it is possible to determine the potential variations produced by the heart beat at any one or all of the apices of Einthoven's equilateral triangle.

It is consequently possible to determine the potential variations produced by the heart beat at any point of the body by leading from this point to the left leg, or the left or right arm, and subtracting the effect produced by the potential variations of this extremity from the recorded curve.

It is possible by this method to free curves obtained by leading from points on or near the heart to points at a distance from it, such as points on the left leg, from the influence exerted by potential variations at the distant electrode.

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Wilson, F. N.: AM. HEART J. 5: 599, 1930.

# A REPORT OF TWO CASES OF LOCALIZED PLEURAL EFFUSION IN HEART FAILURE\*

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## INTRODUCTION

THE first report of localized pleural effusion during the course of heart failure appeared two years ago. This patient, reported by Stewart,<sup>1</sup> developed interlobar pleural fluid during each of four attacks of heart failure. The effusion disappeared with each recovery and its site was found at autopsy. Kiser<sup>2</sup> later reported a similar case in which the lesion was, however, not verified by autopsy. The present report deals with two additional cases, in one of which the existence of the process is confirmed by necropsy.

Search of the literature failed to bring to light any evidence that such a phenomenon had been noted before Stewart's report. Von Jürgensen<sup>3</sup> has made the statement that obliteration of the pleural cavity on one side altered the usual course of bilateral effusion in so far as it limited it to the other side. Upensky,<sup>4</sup> in a report of 16 cases of localized tuberculous pleural effusion, included one, Case No. 15, which from the x-ray photographs alone might have been regarded as due to effusion resulting from heart disease. In the first x-ray photograph the image of a large heart was seen and the shadow of an interlobar effusion. The second, taken after eight months, showed that the fluid had disappeared. The heart appeared much smaller, but since the history is insufficient and since there is lack of data concerning the x-ray technic, it is impossible to judge whether or not the effusion was due to cardiac failure. Freedman<sup>5</sup> in an article on the diagnosis by x-rays of encapsulated effusions appends, to his formal list of causes of encapsulated fluid, all of which were infectious in nature, cardiac failure. He notes, however, that this condition is rare. It seems desirable therefore to report two additional cases exhibiting this phenomenon.

## REPORT OF CASES

CASE 1.†—F. K., Hospital No. 7464, a white male carpenter aged about seventy years, complained of swelling of the feet and shortness of breath. The family history was unimportant. He had always enjoyed general good health. Frequent attacks of tonsillitis early in life led to the removal of his tonsils. Seven years

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†We are indebted to Dr. Clarence de la Chapelle for referring this case to us from the Third New York University Medical Division, Bellevue Hospital, New York.



before admission (July 24, 1930) he had suffered from a febrile illness termed "double pneumonia." An inguinal hernia had been present for seven years.

In May, 1930, while still working regularly, he noticed shortness of breath and swelling of the ankles. Both increased rapidly in severity until he entered Bellevue Hospital where, without medication, edema disappeared during two weeks' rest in bed. On July 24, 1930, he was transferred to this hospital.

The patient was an emaciated elderly white man, senile, and deaf. His temperature was 100° F. His body weight was 72.2 kilograms. He was slightly dyspneic. There was slight cyanosis of the lips and finger nail beds. The general stigmata of arteriosclerosis were present. The peripheral vessels were tortuous and thickened and there was in both eyes a well-marked arcus senilis. The skin was clear, quite loose, and dry. A sebaceous cyst of the scalp was present.

The head was normal in contour. The hearing was markedly diminished, but the ear drums, though thickened, were intact. The pupils were small, round, equal, and regular; they reacted neither to light nor in accommodation. No obstruction of the nose was present. The septum was intact. Many teeth were carious. The tongue was clean and was protruded readily in the midline. The pharynx was negative. The tonsils were large but not injected. The jugular veins were moderately distended. No episternal pulsation or tracheal tug could be felt. The lymph nodes were enlarged. The respiratory excursions were somewhat limited on both sides. The lungs were clear on percussion. The breath sounds were vesicular but a moderate number of moist râles were present at the bases of both lungs posteriorly. The rate of breathing was 32. Over the precordium no pulsations, no thrills nor shocks were felt. The area of relative cardiac dullness was increased, extending 11.5 cm. to the left of the midline in the fifth intercostal space, and 6 cm. to the right in the fourth. The heart sounds were faint but clear. No murmurs were heard.

In an x-ray photograph taken on July 24, 1930, the lung fields were relatively clear (Fig. 1-A). Areas of mottled cloudiness at the bases, more marked on the right side, were present. The root shadows were increased in size. Extending outward and upward from the right hilus to the lateral chest wall at the level of the third rib was a semi-elliptical shadow with a well-defined border, the straight margin of which faced upward. It suggested the presence of fluid encapsulated in the fissure between the upper and middle lobes. The right costophrenic angle was obliterated and the diaphragmatic line was flattened probably due to a small accumulation of fluid or to old adhesive pleurisy. The heart was markedly enlarged, measuring 20 cm. in the transverse diameter—12 to the left, 8 to the right. The width of the chest was 29 cm. The aortic arch was prominent; a well-marked calcified plaque was visible.

The rhythm of the heart was totally irregular and the radial pulse was irregular in both time and force. The rate, counted at the apex was 120, and at the radial artery 104 per minute, resulting in a pulse deficit of 16 beats per minute. The electrocardiogram showed that auricular fibrillation was present and that occasional ventricular premature contractions took place. The systolic blood pressure measured approximately 140 mm. Hg., and the diastolic, 100. The liver was enlarged, extending 5 cm. below the costal margin in the right midclavicular line. It was firm but not tender. The kidneys and spleen were not felt. A large, easily reducible right inguinal hernia was present. The external genitalia were otherwise normal. A small amount of soft edema was present over the shins. There was no clubbing of the fingers and toes. The tendon reflexes were active and equal on the two sides. No patellar or ankle clonus could be evoked. The Babinski test elicited ventral flexion on both sides.

The examination of the urine was negative except for the presence of a very faint trace of albumin. The urinary sediment consisted of deposits of amorphous urates. The Wassermann reaction of the blood was negative.

The diagnosis was general arteriosclerosis, chronic myocarditis, cardiac hypertrophy, auricular fibrillation, congestive heart failure, and interlobar pleural effusion.

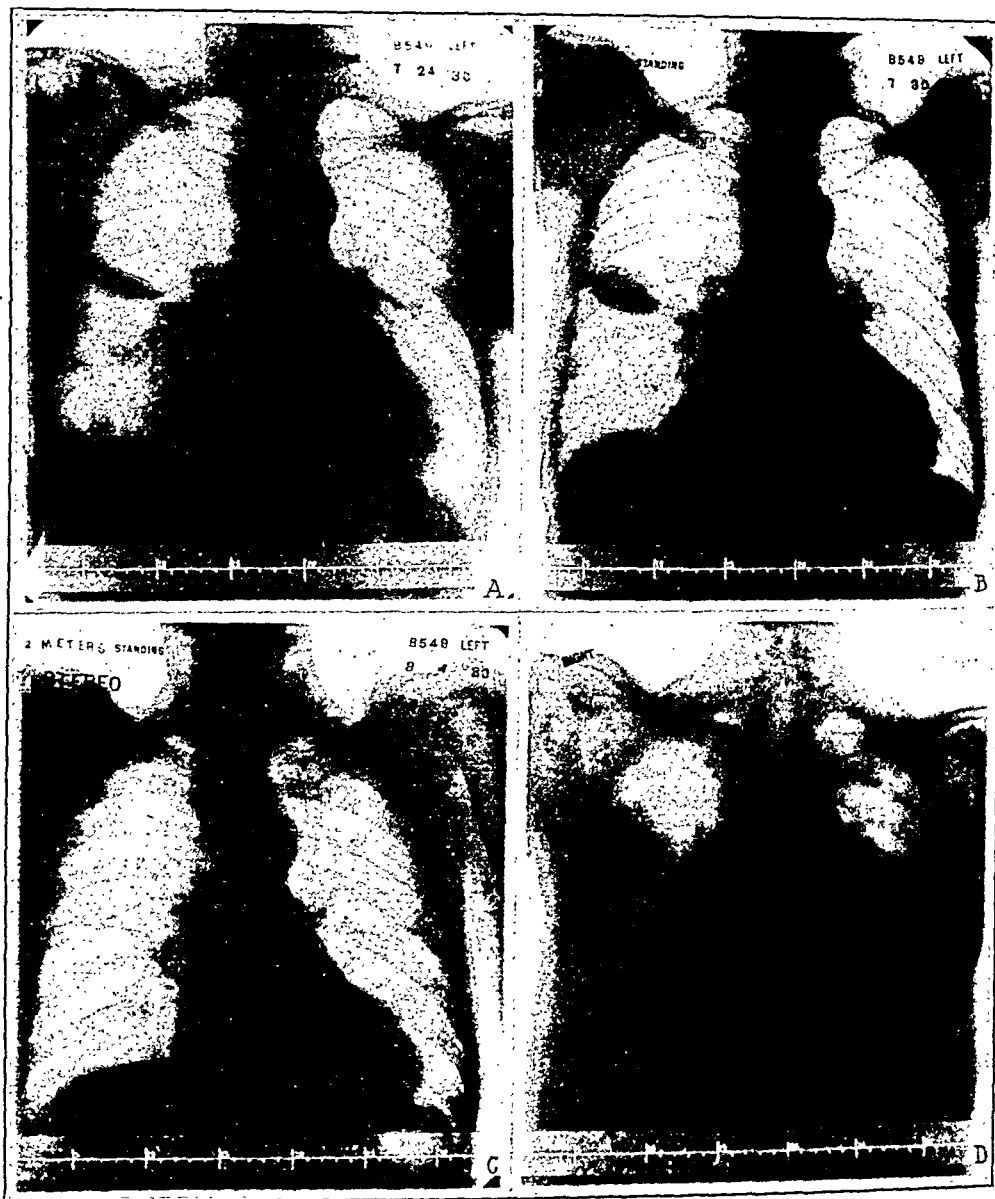


Fig. 1.—Case I. A. X-ray photograph on admission showing size of interlobar effusion when first seen. B. Six days later—effusion increased with increase in signs of heart failure. C. Showing disappearance of the interlobar fluid six days after administration of digitan. D. Post-mortem x-ray picture showing reaccumulated interlobar fluid.

During the first four days in the hospital the condition of the patient grew gradually worse. The cardiac rate increased from 120 to 140 per minute and the pulse deficit from 16 to 36 per minute. The rectal temperature rose by steps from 100.4° to 103.6° F. Although there was a loss of 4 kilograms in body weight

during this period, the urinary output continued low and the amount of edema remained unchanged. Digitan, 1.0 gm. (Merek), was administered within twenty-four hours. The following day (July 30) a second x-ray plate of the chest was made (Fig. 1-B) and showed that the shadow suggesting interlobar pleural effusion had doubled in size, being now ovoid, the upper border as well as the lower being convex. Forty-eight hours after the administration of digitalis, the cardiac rate had fallen to 90, the pulse deficit was only 10 per minute, and the temperature was normal. There was moderate diuresis and six days later (August 4) the patient's body weight had decreased 8 kilograms more. At this time a third x-ray plate (Fig. 1-C) was taken. The shadow had disappeared, leaving only a thin line to mark the site.

From this time until discharge on September 5, one month later, the patient steadily improved, and the temperature remained normal. There was no evidence of heart failure other than slight edema of the ankles which always disappeared by morning. X-ray photographs taken weekly showed that the shadow which had been present in the right upper chest remained absent.

Not quite four weeks after discharge the patient returned (September 30) for examination in a severe attack of heart failure. Extreme dyspnea, intense cyanosis, and anasarca of the lower half of the body were present. Death occurred before he could be examined. An x-ray plate of the chest taken post mortem demonstrated the return of the shadow between the upper and middle lobes of the right lung (Fig. 1-D). It was much larger than during the former attack of failure and was roughly proportional to the greater amount of edema.

The changes in size of the area of the heart in this series of films are interesting. In Fig. 1-A it measures 234.5 sq. cm., the transverse diameter being 20.5 cm. In Fig. 1-B, taken twenty-four hours after completion of the administration of digitalis, it measures 175.5 sq. cm., the transverse diameter being 20 cm. This represents a decrease of 25 per cent from the original size. In Fig. 1-C it measures 17.5 cm. in the transverse diameter and 163 sq. cm. in area. It is noteworthy that the decrease in size had taken place almost entirely in the right side of the heart. The haziness of Fig. 1-D, taken post mortem, makes accurate measurement impossible. The conditions under which it was taken make it, furthermore, incomparable with the other photographs. It is obvious, however, that the heart shadow is much greater than in Fig. 1-C.

*Summary of Post-mortem Examination* (Dr. C. P. Rhoads). The complete anatomical and microscopical diagnosis post mortem is given and a detailed description, pertinent to the subject of this report only, of the heart and lungs.

The left thoracic cavity contained 475 c.c. of rather thick, straw-colored fluid which clotted on standing. The pleural surfaces were smooth and glistening, without adhesions. The right pleural cavity was completely obliterated, the visceral and parietal pleurae being firmly adherent due to dense, fibrous adhesions. The right lung was removed together with the visceral and parietal pleurae. It failed to collapse. When a small incision was made about 4 cm. to the right of the midline, it entered, just under the surface, an opening between the upper and middle lobes, about 1 cm. in diameter, which led to a large oval cavity (Fig. 2), containing about 250 c.c. of straw-colored fluid of medium consistency which clotted on standing. This cavity measured 12 cm. in the greatest diameter horizontally and 8 cm. in the greatest diameter vertically. The cavity was lined with thick, somewhat trabeculated, grayish, ragged, fibrous tissue. The surface of the entire lung could not be separated from the adherent pleurae. A mass of fine to medium coarse, ragged, fibrous adhesions, gray to gray-white in color, covered the lungs, through which the lung parenchyma, blue-gray with black markings, could

be seen. The left lung collapsed partially. The surface was gray-blue, mottled with purple, and showed normal black tracings. The surface on cut section showed a fairly uniform red to red-purple color and exuded a moderate amount of thin, bloody fluid. The bronchi contained a moderate amount of mucus, somewhat blood-tinged. The vessels showed no abnormalities. The surface of the pericardium was smooth and glistening and the cavity contained about 75 c.c. of rather thin, yellowish fluid which clotted on standing. The epicardium anteriorly presented a thickened, somewhat elevated, grayish-white patch of fibrous tissue measuring roughly 8 cm. in diameter. The heart was dilated, extending 15 cm. to the left of the midline and 4 cm. to the right. The color was pale reddish-brown. The consistency was soft. The myocardium was light brown. Five depressed, oval, gray

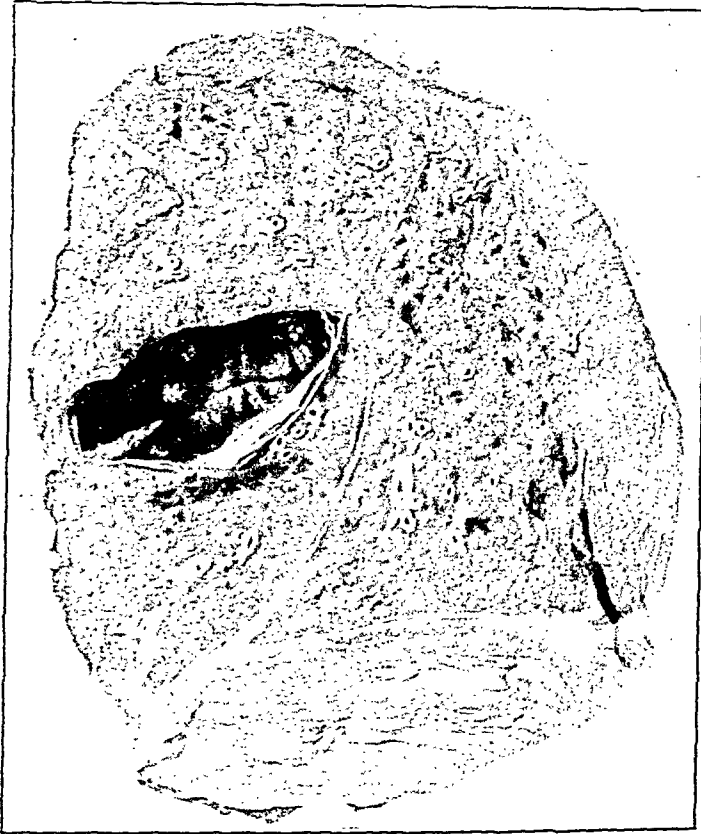


Fig. 2.—Photograph of sectioned lung (Case I). The thickened parietal pleura is well shown. Note normal pleura at site of cavity.

to gray-white areas of scar formation were present on the anterior surface of the left ventricle, from 0.5 to 1 cm. in diameter. They extended a similar distance into the ventricular musculature. At the apex there were scattered grayish areas of fibrosis of small size and indefinite outline. The myocardium of the right ventricle ranged from 0.2 to 0.3 cm., whereas that of the left ventricle ranged from 1 to 1.5 cm. in thickness. The endocardium presented no abnormalities except a few yellowish flecks 2 to 3 mm. in diameter around the base of the mitral valve. The chordae tendineae and the papillary muscles also presented no abnormalities. The tricuspid valve measured in circumference 12 cm.; the pulmonary valve, 9 cm.; the mitral valve, 10.2 cm.; and the aortic valve, 8.2 cm. The coronary arteries presented a very marked degree of atheromatous change, as evidenced by a large number of discrete and coalescent, raised, rather smooth, soft to firm, irregular

yellow to yellow-white plaques, most marked near the aorta and decreasing in frequency as the apex of the heart was approached, although very little of the intimal surface was spared. Ulceration was rare.

The aorta also presented a very marked degree of atheromatous change which was most marked at the arch, sparing the tissue near the aortic valve almost completely. The arch and the thoracic and abdominal portions of the aorta presented an enormous number of roughly circular or oval, raised, smooth, soft to very firm, yellow to yellowish-white areas. Those in the arch were extremely hard and inflexible, whereas the degree of calcification became less as one proceeded caudally. At about the level of the twelfth thoracic vertebra the intima of the aorta was ulcerated, the base of the ulcer presenting a depressed ragged surface 0.5 cm. in diameter which communicated with the adventitia. Superficial ulcerations were present elsewhere, showing a granular, reddish, hard base, surrounded by raised, smooth, thickened aortic intima.

On microscopical examination, the lungs presented no abnormality. In the heart there was extensive replacement of the myocardium by connective tissue. In the aorta there were subintimal collections of lipoid and cholesterol crystals. There was intimal proliferation. At one point there was an ulcerated necrotic plaque, the intima of which was thickened and had ruptured. There was infiltration with lipoid material. The vasa vasorum presented marked inflammatory changes. Besides these changes, there were the usual cholesterol subintimal infiltrations and intimal thickenings. At other portions there were typical atheromatous plaques with calcification together with marked perivascular infiltration in the adventitia. The coronary arteries exhibited very marked infiltration with cholesterol crystals and vacuolated cells. The vasa vasorum showed perivascular infiltration. The aortic and mitral valves presented no abnormalities.

Examination of the fluid obtained from the oval pleural cavity was as follows: sp. gr. 1.010, albumin 0.9 gm. per liter, leucocytes, 32 cells per c.c. On cultivation there was isolated a hay bacillus. This fluid was identical with that found free in the left pleural cavity.

As in Stewart's case, the whole right pleural cavity was obliterated, the pleura lining the sac of fluid being the only relatively normal pleura left. There were no areas of inflammation in the lungs; the negative cultures, the low specific gravity, and albumin content of the fluid showed that it was a transudate. The fluid was undoubtedly the result of cardiac failure.

CASE 2.—E. K., Hospital No. 4464, was a man fifty-seven years of age. He was always a vigorous active person in good health. No attacks of tonsillitis, rheumatic fever, or chorea were recalled. He suffered from three Neisserian infections as a young man, but no history of syphilis was obtained. His wife and two children were living and well.

In the spring of 1920, two years prior to the first admission, he experienced dyspnea on rapid walking and on climbing stairs. Three months later swelling of the ankles appeared in the evening. A physician then prescribed digitalis and improvement followed. Except for an occasional rest of two or three days a month he continued to work as formerly. Edema and dyspnea remained approximately at the same degree for a year. In November, 1921, dyspnea and edema began to increase in severity until three months later dyspnea was severe even at rest and edema extended to the thighs. In January, 1922, the abdomen began to enlarge.

He had not experienced palpitation, precordial pain, or cough. Cyanosis had not been observed. Bleeding from hemorrhoids had been present for two years, since the onset of the illness.

On February 2, 1922, at the time of admission to the hospital the state of nutrition and muscular development were good. Moderate orthopnea and slight dyspnea were present. The temperature was  $100.4^{\circ}$  F. (rectal). The skin was



Fig. 3.—Case II. A. X-ray photograph showing effusion over the right upper lobe occurring during first attack of heart failure. B. Twenty-five days later—interlobar fluid disappeared. C. Eight years later during second attack of heart failure showing a precisely similar effusion. D. Five days after C following recovery from second attack of heart failure.

pale. The lips, ears, and finger tips were faintly cyanotic. The examination of the ears was negative. The teeth had been much treated; pyorrhea alveolaris was present. The tonsils were not enlarged. The nasal septum was intact. The extraocular movements were well performed. The pupils were round, equal and regular, and reacted normally to light and in accommodation. The jugular veins were

somewhat distended. There was no enlargement of the thyroid or of the superficial lymph glands. A tracheal tug was not present. The right half of the chest was flattened when compared with the left and the respiratory movements were somewhat limited. Scoliosis of the vertebral column in the thorax, convexity being to the left, was present, and was well exhibited in an x-ray photograph taken on February 3, 1922. Percussion demonstrated marked dullness below the angle of the scapula on the right side posteriorly; in this region, vocal fremitus and the breath sounds also were diminished. Crackling râles were heard at both bases. There was no area of paravertebral dullness. On palpation, localized pulsation at the base of the heart and a systolic shock at the apex were felt. The relative cardiac dullness extended 11 cm. to the left of the midline in the fifth intercostal space and 4.5 cm. to the right in the fourth. The pulse rate was 90; the respirations were 24 per minute. The systolic blood pressure measured 124 mm. Hg., the diastolic, 68. Owing to the presence of scoliosis and the consequent deformity of the chest, the shape of the heart was distorted. It seemed to be enlarged, but exact measurement was impossible. The rhythm was totally irregular as demonstrated in electrocardiograms. The sounds were vigorous and especially so were the first sound at the apex and the second sound over the pulmonic area. A protodiastolic gallop was heard over the whole precordium. No murmurs were heard. The root shadows were of increased density and the outline of the diaphragm was hazy. Of particular interest was a zone of increased density 1.5 cm. in diameter surrounding the upper lobe and lying against the lateral chest wall (Fig. 3-4). There was a convex widening of this shadow at the level of the third intercostal space anteriorly, bulging inward for 2.5 cm. at a point where one might expect the lateral end of the interlobar fissure between the upper and middle lobes to be. The shadow suggested encapsulated fluid or a markedly thickened pleura. The radial pulse was irregular and quick. The peripheral arteries were palpable but not markedly thickened. The abdominal cavity was distended with fluid; the liver edge was felt at a level of 2 cm. below the costal margin in the mammillary line. The spleen was easily palpable. General anasarca of the lower half of the body was present. There were numerous varicose veins in the calves of the legs.

The specific gravity of the urine varied between 1.027 and 1.013. The tests for sugar were negative. Albumin, present in moderate amounts on admission, disappeared by the end of the third week. Red and white blood cells were no longer observed at the end of the third week after admission to the hospital. The urea nitrogen in the blood measured 59 gm. per liter. The phenolsulphonephthalein excretion in two hours was 42 per cent.

The count of the red blood cells was 4,500,000 and of the white blood cells 12,800 per cubic mm. A test for the oxygen capacity of the blood showed that there was 6.85 gm. of hemoglobin per 100 c.c. In a differential count the polymorphonuclear neutrophils were 77 per cent; polymorphonuclear eosinophiles 2 per cent; polymorphonuclear basophiles 1 per cent; monocytes and lymphocytes 20 per cent. The reaction of the blood serum on February 11 to the Wassermann test in cholesterin antigen was ++ and ± in alcoholic antigen with ice box fixation; on March 23, in cholesterin antigen it was ++++ and +++ in alcoholic antigen; on April 28 in cholesterin antigen with ice box fixation, it was ++++ and negative in alcoholic antigen.

During the first three days in the hospital (February 2 to February 5) the temperature rose from 100.6° to 104° (rectal). A cough developed and mucopurulent sputum tinged with blood was expectorated from which was cultured a Type IV Pneumococcus. The cardiac and radial pulse rates rose from 106 and 96

to 140 and 104, respectively. On the fourth and fifth days (February 6 and February 7) digitan, 1.2 gm. (Merck), was given within thirty-six hours. Subsequently the patient was kept under the influence of digitalis by the administration of small doses. Although the cardiac rate was slowed by digitalis, there resulted very little increase in the urinary output, slight loss of weight, and no disappearance of edema. The use of theocin was also without diuretic effect. Thoracentesis was performed on two occasions. A very resistant pleura was encountered but fluid was not obtained. The temperature fell slowly to 101°.

On February 13, the rhythm of the heart abruptly became normal. Two days later, after 0.5 gm. more of digitan had been given, excellent diuresis occurred. At this time the x-ray photograph was identical with the one taken on admission (Fig. 3-A). During the next ten days (to February 23) the body weight fell from 72.8 to 65.2 kg. and edema, ascites, and breathlessness disappeared. A few moist râles were still heard at the bases of the lungs. An x-ray photograph taken on February 21 showed that the shadow about the upper lobe had diminished to one-half its width, while in one taken on February 28 (Fig. 3-B) it had completely disappeared.

Until April 28, 1922, he remained in a state of cardiac compensation, the heart rhythm being regular. Potassium iodide and mercuric inunctions were given. Those teeth showing abscesses at the roots were extracted. When he was discharged, a moderately enlarged liver and spleen were the only apparent residua of his attack of heart failure. An x-ray photograph taken on discharge showed that the shadow at the periphery of the right upper lobe had not returned.

He was examined at bi-monthly intervals until February of 1924. During 1923 the rhythm of the heart reverted to that of auricular fibrillation but with the administration of digitan (Merck), adequate compensation was maintained. Although the liver remained large and slight pitting edema of the ankles was sometimes present, he continued at active work. He was not examined during the next four years, but in 1928 returned, stating that he had been quite well during the whole interim. The rhythm of the heart was again normal. X-ray photographs taken during the period of six years had not shown a return of the shadow about the right lobe.

He disappeared again for two years, but on April 23, 1930, eight years after the first attack of heart failure, and ten years after the onset of the first symptoms, he returned to the hospital suffering from a moderately severe attack and was admitted for the second time.

He had worked steadily until two weeks before when dyspnea reappeared. Slight pitting edema, which had been present off and on for eight years, slowly increased. The abdomen had also enlarged, and he became aware of a sense of oppression in the epigastrium.

The physical examination and, indeed, the course of his illness were so extraordinarily similar to those of his first admission, except that the attack was not so severe, that a detailed description of them is unnecessary. Only relevant phenomena or significant differences from those present formerly need be mentioned.

The general physical examination remained unchanged. The bases of the lungs were fixed. Râles were heard at both. The size of the heart was approximately as before; the sounds were clear, the rhythm was totally irregular and an electrocardiogram confirmed the fact that auricular fibrillation was present. No murmurs were heard. The liver and spleen were enlarged; ascites was present. Edema was much less marked, extending only to the knees.



The Wassermann reaction of the blood was still positive but only when cholesterinized antigen was used. The count of the white blood cells was not increased.

In general the x-ray photograph resembled those made during his visits to the clinic. In addition, adhesions at the bases were present and a well-defined opacity in the left lower lobe was noted. The shadow surrounding the right upper lobe noted during his first failure (Fig. 3-A) was absent.

Fluid was not obtained on thoracentesis on April 28. In an x-ray photograph taken on May 1, the shadow at the right base persisted. At the periphery of the right upper lobe an opaque shadow bulging into the region of the interlobar fissure now appeared, identical in outline with that seen eight years before (Fig. 3-C). On May 3, fever of 100.4° F. occurred, increasing the following day to 101.8°, accompanied by cough and expectoration of bloody sputum. No change, however, was observed on examination of the chest. By May 7, the temperature had entirely subsided, the cough had improved, edema and dyspnea had decreased. An x-ray photograph taken on May 6, the last day of fever (Fig. 3-D), showed that the shadow about the right upper lobe had also disappeared. When the patient was discharged on June 14, an enlarged liver and spleen were the only signs remaining of heart failure. He remains well and at work.

#### SUMMARY AND CONCLUSIONS

Two cases in addition to those already reported are described in this report in which, with recurrent attacks of heart failure, localized opaque areas in x-ray plates in the right upper half of the thoracic cavity appeared before improvement of the signs of heart failure began, and disappeared with the disappearance of edema and general recovery. In both cases similar shadows reappeared with the second attack. One of the patients died during the second attack. In this case, autopsy showed that the whole right pleural cavity, with the exception of the small portion between the right upper and middle lobes which constituted the site of effusion, was obliterated. Enclosed between these surfaces of normal pleura about 250 c.c. of fluid, having all the characteristics of a transudate, were found.

In all the cases, including the two previously reported, it is noteworthy that the encapsulated pleural effusion occurred during the first attack, and that the pleura was thickened on the side of the effusion in three of the four. In two, at autopsy, the whole pleural cavity was obliterated save in the region of the effusion. In the third, that the pleura was thickened was demonstrated by the difficulty of performing thoracentesis. Only one case gave a history of previous pulmonary infection.

It seems likely therefore that the occurrence of localized pleural effusions like these is dependent on the existence of extensive adhesive pleurisy antecedent to the development of heart failure.

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## THE INCIDENCE OF HEART DISEASE AND OF THE ETIOLOGICAL TYPES IN A SOUTHERN DISPENSARY\*

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IN VIEW of the prominence that organic heart disease has assumed as a cause of death in the United States in the past few decades, the prevention of cardiovascular diseases has become one of the outstanding problems of preventive medicine. Material accomplishments in the direction of the prevention of heart disease cannot be anticipated until the etiological factors are clearly defined and the accessory elements of predisposition recognized. For that reason any contribution to our present knowledge of the causal agencies of heart disease is at this time most desirable. Important additions to our information on the subject have been made by recently reported statistical studies on the incidence of heart disease and of the various etiological types in different sections of the United States. With the successive appearance in the literature of reports of such statistical studies from widely separated sections of the country, it becomes more and more obvious that such factors as climate, geographical location, race, economic status, and social strata exert a profound influence on the unknown causal agents of heart disease in general and the various etiological types in particular.

Among the contributions to the statistical data on the incidence of heart disease and of the etiological types is the report of Stone and Vanzant,<sup>1</sup> who in 1927 reported an analysis of 915 cases of organic heart disease seen in all Services of the John Sealy Hospital of Galveston over a period of seven years. The value of this study is enhanced by the fact that it included private as well as charity patients, two entirely different social strata therefore being represented. However, whether or not this report gives a fair index of the incidence of the various etiological types of heart disease in this community is open to question for the reasons that follow. First, the majority of patients with heart disease do not enter the charity wards until they are in dire need of hospitalization. Thus it is apparent that many patients with heart disease are not included in a study confined to hospital cases. Also, as will be pointed out later, certain etiological types of heart disease produce greater disability than other types and consequently under the circumstances will receive an unfair representation in the hospital wards. Second, because of the limited facilities for negro charity patients as compared

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with white patients in the John Sealy Hospital, an accurate incidence study of the community population is impossible for, from what is to follow, it is evident that organic heart disease is much more prevalent in the negro than in the white race. The truth of the statement by White and Jones<sup>2</sup> that "no single series of patients—private, hospital, or clinic—gives a correct incidence of heart disease" should be reiterated.

#### MATERIAL STUDIED

In the seven and one-half year interval dating from January 1, 1924 to July 15, 1931, 49,880 new patients were seen in all Divisions of the Out-Patient Department of the John Sealy Hospital. Of this number 10,188, or 20.4 per cent, came under observation in the Medical Division. This latter group was composed of 4,252 (41.7 per cent) white persons of whom 2,570 were males and 1,682 females; and 5,936 (58.3 per cent) negroes of which 3,188 were males and 2,748 females. Of the 10,188 patients seen in the Medical Division 1,660 were found to have organic heart disease. These 1,660 cases of heart disease constitute the basis for this study and include only those patients who presented definite evidence of organic heart disease as determined by the history and physical examination, and confirmed by the Wassermann reaction, teleroentgenogram, electrocardiogram, and renal function tests when indicated. Those cases in which the diagnosis of heart disease remained questionable, after special diagnostic measures had been resorted to, are not included in this study.

This group of 1,660 patients with organic heart disease with reference to race was composed of 1,172 (70.6 per cent) negroes and 488 (29.4 per cent) white patients; with reference to sex, 719 (43.2 per cent) females and 941 (56.8 per cent) males; and with reference to both race and sex, white females 11.3 per cent, white males 18.1 per cent, negro females 32 per cent, and negro males 38.6 per cent.

#### CRITERIA EMPLOYED FOR ETIOLOGICAL CLASSIFICATION

In cataloguing the cases of heart disease according to etiology, as simple a classification as possible was employed. Multiple etiological factors were present in a number of instances, and under such circumstances the final grouping of the case was dependent upon what causative factor was considered to be the primary condition. The criteria for the diagnosis of the etiological types of heart disease as proposed by the Heart Committee of the New York Tuberculosis and Health Association<sup>3</sup> were used, with the modifications indicated below.

*Hypertensive Heart Disease.*—Included in this category are those cases which presented a persistent elevation of both the systolic and diastolic blood pressures (above 150 mm. Hg. systolic and 95 mm. Hg. diastolic) associated with demonstrable enlargement of the heart either

without impairment of renal function or with evidence that such impairment was secondary to a preëxisting hypertension. Pregnant women fulfilling the above criteria were not included in this group. Realizing that the vessel trauma incident to a long standing hypertension eventually results in arteriosclerosis, we placed those patients fulfilling the above enumerated criteria in this group regardless of the presence of arteriosclerosis. It is felt that the type of blood pressure elevation and the character of the resulting vessel change are sufficiently distinctive to exclude the possibility of arteriosclerosis being the primary factor in the production of the heart disease. In other words, all patients placed in this group were considered as having essential hypertension with or without its complications, the presence or absence of the latter depending largely on the duration of the blood pressure elevation.

*Arteriosclerotic Heart Disease and Coronary Artery Disease.*—There were placed in this group those patients who exhibited definite evidence of arterial change, the senescent type of arteriosclerosis in the large majority of instances, usually with cardiac enlargement, with or without elevation of the blood pressure, and with definite evidence of a diminished cardiac reserve. In those cases exhibiting hypertension a careful study of numerous blood pressure determinations was made before placing them in this group. In all instances the diastolic blood pressure was found to be essentially normal or only slightly elevated in proportion to the systolic pressure, which was constantly high, in some cases the elevation being moderate, in others marked. It is felt that arteriosclerosis with the consequent rigidity of the vascular tree, so characteristic of old age, is responsible for this type of blood pressure elevation which is entirely different in both pathogenesis and character from that type previously discussed. It follows from these criteria that a majority of the patients in this group were of advanced age. However, there are also included in this category a fair number of patients in middle life exhibiting clinical evidence of myocardial weakness and failure in whom coronary artery disease was thought to be the etiological agent. The clinical picture portrayed by this type of heart disease manifestly lacks discreteness. In our series reliance was placed mainly on the past history of a probable coronary thrombosis, along with electrocardiographic evidence, or on electrocardiographic evidence alone in arriving at a diagnostic decision in these cases.

*Syphilitic Cardiovascular Disease.*—In the diagnosis of this type of heart disease, emphasis was placed largely on the discovery of one of the characteristic structural changes; namely, aortitis, aneurysm, or aortic insufficiency, or a combination, in the presence of a positive Wassermann reaction, of a positive history, or of lesions in other parts of the body pathognomic of a syphilitic infection. In all cases of aortic regurgitation, especially in young persons, a history of the presence or absence of past attacks of rheumatic fever, chorea, or recurrent tonsil-

litis was taken into consideration. A surprisingly small number of cases of syphilitic aortitis are represented in our series. It is our belief that this is largely due to the fact that syphilitic aortitis in the negro is only rarely attended by the classical symptoms of this condition and, as a result, these patients are not seen at this early stage of their disease. Aware of the difficulty in the diagnosis of this particular type of cardiovascular syphilis, especially if the symptoms are lacking and a moderate hypertension exists, we adhered to very rigid criteria in the compilation of this group. In patients fulfilling the criteria for other types of heart disease, the presence of a positive Wassermann reaction did not alter such a classification.

#### INCIDENCE OF HEART DISEASE

A review of the data presented in Table I indicates that organic heart disease occurs in 3.3 per cent of all patients seen in the Out-Patient Department of the John Sealy Hospital, and in 16.3 per cent of all patients seen in the Medical Division. A consideration of the incidence of organic heart disease in reference to race in the patients observed in the Medical Division reveals that 19.7 per cent of the negroes had heart disease, whereas only 11.5 per cent of the white patients were similarly afflicted. It follows from this analysis that in those patients who visit an out-patient department, heart disease occurs one and seven-tenths times more often in the negro than in the white race.

TABLE I  
INCIDENCE OF ORGANIC HEART DISEASE

|  |        |        |       |        |
|--|--------|--------|-------|--------|
| Number of Out-Patient Department Cases               | 49,880 |        |       |        |
| Number of Medical Cases                              | 10,188 |        |       |        |
| Number of Cases of Organic Heart Disease             | 1,660  |        |       |        |
| Percentage of Organic Heart Disease in All Cases     | 3.3    |        |       |        |
| Percentage of Organic Heart Disease in Medical Cases | 16.3   |        |       |        |
| Classification of Cases According to Race and Sex:   |        |        |       |        |
|  | White  |        | Negro |        |
|  | Male   | Female | Male  | Female |
| Medical Cases  | 2,570  | 1,682  | 3,188 | 2,748  |
| Heart Cases  | 301    | 187    | 640   | 532    |
| Percentage Showing Heart Disease                     | 11.7   | 11.1   | 20.1  | 19.1   |
| Percentage of Organic Heart Disease in Total Whites  | 11.5   |        |       |        |
| Percentage of Organic Heart Disease in Total Negroes | 19.7   |        |       |        |
| Percentage of Organic Heart Disease in Total Males   | 17.8   |        |       |        |
| Percentage of Organic Heart Disease in Total Females | 13.3   |        |       |        |

With reference to sex, 17.8 per cent of the males and 13.3 per cent of the females coming to the Medical Division had heart disease, indicating that in this clinic organic heart disease is one and three-tenths times of greater incidence in the male than in the female. Further resolution of this table discloses that 20.1 per cent of the negro males,

11.7 per cent of the white males, 19.1 per cent of the negro females, and 11.1 per cent of the white females had organic heart disease. Considering all types of heart disease the sex incidence in the respective races is practically the same, there being only a slight discrepancy between the negro males and females.

#### INCIDENCE OF THE ETIOLOGICAL TYPES

Reference to Table II reveals that of the 1,660 patients with heart disease 948 (57.2 per cent) were of the hypertensive type; 335 (20.2 per cent) were arteriosclerotic; 212 (12.7 per cent) were placed in the syphilitic group; 57 (3.4 per cent) permitted classification as of rheumatic origin; 41 (2.5 per cent) fell into the thyrotoxic class; 12 (0.7 per cent) were of congenital origin; 39 (2.3 per cent) were impossible of classification; and 16 (1.0 per cent), including 6 cases of subacute bacterial endocarditis, 8 of emphysema heart disease, and 2 of acute and chronic pericarditis, were classified as miscellaneous. There

TABLE II  
FREQUENCY OF HEART DISEASE IN THE VARIOUS ETIOLOGICAL GROUPS

| TYPE             | NUMBER<br>OF<br>CASES | PER<br>CENT | WHITE |        | TOTAL | NEGRO |        | TOTAL |
|------------------|-----------------------|-------------|-------|--------|-------|-------|--------|-------|
|                  |                       |             | MALE  | FEMALE |       | MALE  | FEMALE |       |
| Hypertensive     | 948                   | 57.2        | 95    | 112    | 207   | 338   | 403    | 741   |
| Arteriosclerotic | 335                   | 20.2        | 140   | 35     | 175   | 125   | 35     | 160   |
| Syphilitic       | 212                   | 12.7        | 31    | 2      | 33    | 132   | 47     | 179   |
| Rheumatic        | 57                    | 3.4         | 18    | 18     | 36    | 10    | 11     | 21    |
| Thyrotoxic       | 41                    | 2.5         | 1     | 13     | 14    | 6     | 21     | 27    |
| Congenital       | 12                    | 0.7         | 1     | 2      | 3     | 5     | 4      | 9     |
| Miscellaneous    | 16                    | 1.0         | 8     | 0      | 8     | 6     | 2      | 8     |
| Unknown          | 39                    | 2.3         | 7     | 5      | 12    | 18    | 9      | 27    |
| Total            | 1,660                 | 100.0       | 301   | 187    | 488   | 640   | 532    | 1,172 |

were included in this series 11 cases of angina pectoris, all complicating some other type of heart disease and all occurring in white patients. These statistics make it obvious that in this particular community we are concerned largely with three types of heart disease; namely, the hypertensive, the arteriosclerotic, and the syphilitic, these three groups constituting approximately 90 per cent of all cases of organic heart disease coming under observation. Rheumatic heart disease, an extremely important etiological group in many sections of the United States, in this locality plays a very minor rôle.

#### HYPERTENSIVE HEART DISEASE

In this locality, patients with this type of heart disease constitute by far the largest etiological group, 948 cases or 57.2 per cent of all the cases of organic heart disease. Of these 948 patients, 207 (12.4 per cent) were white patients and 741 (44.6 per cent) were negroes.

The incidence of hypertensive heart disease in the patients coming to the Medical Division is 12.5 per cent for the negro and 4.9 per cent for white patients, from which it seems to follow that the hypertensive type of heart disease is about two and one-half times of greater incidence in the negro than in the white race. Similar analysis of these data in a consideration of the influence of sex on the incidence of this etiological type reveals that of the 948 patients constituting this group 515 (31 per cent) were females and 433 (26.1 per cent) were males, the incidence for the patients seen in the Medical Division being 11.6 per cent for females and 7.5 per cent for males. Obviously in this clinic hypertensive heart disease is of one and one-half times greater incidence in females than in males. The greater incidence of hypertensive heart disease in the female is not generally appreciated, several standard textbooks stating the opposite to be true. Analysis of these same data as regards both race and sex reveals that the incidence of hypertensive heart disease in the patients coming to the Medical Division was as follows: negro males 10.6 per cent, white males 3.7 per cent, negro females 14.7 per cent, and white females 6.6 per cent. These figures suggest that in this type of heart disease the incidence is three and one-tenth times as great in the negro male as in the white male, and two and two-tenths times of greater incidence in the negro female than in the white female. It is further indicated that essential hypertension is one and eight-tenths times of greater prevalence in the white female than in the white male, whereas in the negro race the incidence in the female is only one and four-tenths times greater than that in the male.

#### ARTERIOSCLEROTIC HEART DISEASE

Patients with this type of heart disease comprise the second largest group in this series, 335 cases or 20.2 per cent of all the heart cases. Approximately 60 per cent of these cases exhibited hypertension. Of these 335 cases, 175 (10.5 per cent) were white patients and 160 (9.6 per cent) were negroes. The incidence in the medical cases for the arteriosclerotic type of heart disease with reference to race is 2.7 per cent for negroes and 4.1 per cent for white patients, from which it follows that this type of heart disease occurs one and one-half times more frequently in the white than in the negro race. Further analysis of these data in a consideration of the influence of sex on the incidence of this type of heart disease discloses that of these 335 patients there were only 70 (4.2 per cent) females as compared with 265 (15.9 per cent) males, the incidence in the medical cases being 1.6 per cent for females and 4.6 per cent for males. Manifestly this etiological type of heart disease occurs approximately three times as often in males as in females.



## SYPHILITIC CARDIOVASCULAR DISEASE

Of the 1,660 cases of organic heart disease, 212 or 12.7 per cent fell into this category. With reference to structural changes this group is further divisible as follows: 162 cases of aortic regurgitation of which 102 occurred in negro males, 32 in negro females, 25 in white males, and 2 in white females; 37 aneurysms of which 24 occurred in negro males, 7 in negro females, and 6 in white males; 14 cases of syphilitic aortitis all of which occurred in the negro race, 6 in the males and 8 in the females. Considering all of the patients seen in the Medical Division of the Out-Patient Department, the racial incidence for this type of heart disease is 3 per cent for negroes as compared with 0.7 per cent for the white race. Conversely this type of cardiovascular disability is four times as frequent in the negro as in the white medical patient. A consideration of the incidence with reference to the various structural changes reveals that aneurysms occur with greater frequency in the negro as compared with the white race than does aortic insufficiency. A consideration of these statistics from the aspect of the relation of sex to the incidence of this etiological type reveals that among the medical patients the incidence for males is 2.8 per cent while for females it is only 1.1 per cent, indicating that in this locality at least this type of heart disease is of two and one-half times greater incidence in the male than in the female.

## RHEUMATIC HEART DISEASE

The number of patients included in this series suffering with this type of heart disease is too small to justify the arrival at any conclusions as regards the influence of race or sex on the incidence of this etiological type. In this locality rheumatic heart disease like the arteriosclerotic type appears to occur more frequently in the white race than in the colored. As regards sex, the incidence is slightly higher in the female than in the male.

The low incidence of rheumatic heart disease in this community is readily explainable on the basis of the rare occurrence of the rheumatic series of infections in the South, a phenomenon in which climate appears to play a large part.

## THYROTOXIC HEART DISEASE

In this clinic where hyperthyroidism is not frequently seen, this type of heart disease necessarily constitutes a relatively small group, 41 cases or 2.5 per cent of all the heart cases. It is, however, interesting to note that in this small group, too small perhaps to be of any comparative value, the incidence for this type of heart disease is greater in the negro (0.4 per cent) than in the white race (0.3 per cent). As would be expected, the incidence in females is greater than that in the males.

The infrequency of endemic goiter in this locality because of its situation on the seacoast seems to be an adequate explanation for the low incidence of thyrotoxic heart disease here as compared with more inland regions.

#### UNKNOWN HEART DISEASE

The group impossible of classification constituted 2.3 per cent of the heart cases. It is very probable that a fair number of the cases catalogued in this group formerly had hypertension, in view of the fact that they presented evidence of marked enlargement of the heart in the absence of valvular disease, a finding so characteristic of the hypertensive type, and a complete absence of other discernible etiological factors. Also included in this group are a number of cases, practically all negro males, who exhibited marked cardiac enlargement, congestive heart failure in the majority of instances, a strongly positive blood Wassermann reaction, and a striking absence of the characteristic structural lesions of syphilitic heart disease. Necropsy on a number of these cases shed no further light on an etiological diagnosis. It is very likely that they belong in the syphilitic group.

#### COMPARISON

Few statistics are available to enable a comparison of the incidence of heart disease in various sections of the United States to be made. Davis and Thoroughman<sup>4</sup> reported that 3.7 per cent of all admissions to the University Division of the Grady Hospital of Atlanta, Georgia and 21.7 per cent of those admitted to the Medical Services had organic heart disease. In an interpretation of these data it should be remembered that only negroes are admitted to this hospital. In Stone and Vanzant's series<sup>1</sup> 3.6 per cent of all hospital admissions and 16 per cent of all admissions to the Medical Services (of the John Sealy Hospital in Galveston) had organic heart disease. Coffen<sup>5</sup> of Portland, Oregon reported that of 13,258 medical patients admitted to six different hospitals 26 per cent were afflicted with heart disease.

The available statistical matter on the incidence of the etiological types of heart disease accumulated from widely separated sections of the country should lend itself to a very valuable as well as interesting study in comparison. However, owing to the discrepancy of the diagnostic criteria employed for certain types of heart disease by the different authors, an exact comparison is made very difficult. The fairly universally accepted criteria for the diagnosis of syphilitic, rheumatic, and thyrotoxic heart disease permits accurate comparison of these etiological types. The difficulty arises when a comparison of the arteriosclerotic, the coronary artery disease group, and the hypertensive groups is attempted, as in many instances these groups are combined and designated as arteriosclerotic or as arteriosclerotic plus hypertension.

TABLE III

COMPARISON OF REPORTED STATISTICS

|                                 | No. cases | VIRGINIA | NEW YORK CITY | NEW ENGLAND | ROCKY MOUNTAINS | TEXAS             |            | AVERAGE |
|---------------------------------|-----------|----------|---------------|-------------|-----------------|-------------------|------------|---------|
|                                 |           |          |               |             |                 | STONE AND VANZANT | OURS       |         |
|                                 |           | 300<br>% | 1,000<br>%    | 2,421<br>%  | 867<br>%        | 915<br>%          | 1,660<br>% | %       |
| Rheumatic                       |           | 15.6     | 42.7          | 29.3        | 44.0            | 7.3               | 3.4        | 5.3     |
| Arteriosclerotic                |           | 32.4     | 22.3          | 26.3        | 21.1            | 13.7              | 20.2       | 16.9    |
| Hypertensive                    |           | 32.6     | —             | 21.7        | 14.9            | 47.7              | 57.2       | 52.4    |
| Syphilitic                      |           | 7.8      | 8.6           | 2.7         | 1.1             | 19.3              | 12.7       | 16.0    |
| Thyroid                         |           | 2.6      | —             | 2.1         | 9.3             | 1.3               | 2.5        | 1.9     |
| Angina pectoris                 |           | 6.6      | —             | 10.9        | —               | 2.3               | —          | —       |
| Congenital                      |           | 0.7      | —             | 1.1         | 1.1             | 0.7               | 0.7        | 0.7     |
| Unknown                         |           | 1.6      | 17.8          | 2.2         | 7.3             | 4.9               | 2.3        | 3.6     |
| Miscellaneous                   |           | —        | 8.6           | 1.6         | 0.9             | 1.3               | 1.0        | 1.1     |
| Subacute bacterial endocarditis |           | —        | —             | 1.4         | 0.2             | 1.5               | 0.3        | 0.9     |

The use of that type of classification does not permit further segregation of the hypertensive cases into those in which the arteriosclerosis was a secondary change and those in which the condition was primary. In this communication an attempt has been made to distinguish between the different types of hypertension and to catalogue them in separate groups.

In Table III, taken from the report of Viko<sup>6</sup> with the addition of data accumulated by this study, there is presented a comparison of the relative incidence of the etiological types of heart disease in widely separated sections of the United States.

As was emphasized in the introduction of this communication, the incidence of heart disease, particularly the relative incidence of the etiological types, in a locality will vary, depending upon the source of the material—that is whether the statistics were gathered from a study of private, hospital, or dispensary patients. Reference to Table III reveals a discrepancy in the data presented by Stone and Vanzant and the results obtained from our study. This discrepancy confirms the truth of the statements made in the introduction. The difference is disclosed mainly in the comparison of the hypertensive group (47.7 per cent compared with 57.2 per cent), the arteriosclerotic (13.7 per cent compared with 20.2 per cent), and the syphilitic (19.3 per cent compared with 12.7 per cent). These differences are readily explainable by the fact that the cardiac disability incident to the hypertensive and the arteriosclerotic types is seldom as extreme as in the syphilitic group and consequently a fewer number of the former groups demand hospitalization as compared with the latter. Another factor which accounts for the greater number of hypertensive cases in our series is the larger percentage of negroes in our study who, as we have already shown, have a much higher incidence of hypertensive heart disease than do white patients.

As regards a comparison of the incidence of the etiological types of heart disease in this locality with similar statistics from other sections of the country, our results do not materially alter the conclusions drawn by Stone and Vanzant, but further emphasize the high incidence of syphilitic and hypertensive heart disease and the extremely low incidence of rheumatic heart disease. The high incidence of these two types of heart disease is accounted for largely by the factor of race, a large number of negroes being included in both studies.

Perhaps the most outstanding fact that appears from this study is the extremely high incidence of organic heart disease as a whole in the negro as compared with his white brother. One becomes even more impressed following a comparison of the various etiological types in the two races. It is generally known that syphilitic heart disease is of much higher incidence in the negro than in the white race, usually attributed to the fact that syphilis is of greater prevalence in that race.

However, it is quite possible that this is not the only factor involved. On the contrary, it is not generally recognized that hypertensive heart disease is of so much greater prevalence in the negro race, being in this study two and one-half times more frequent. This rather startling fact opens a fertile field for investigation. Were it possible definitely to ascertain the reasons for this marked discrepancy, the riddle of hypertension would be nearer solution. Arteriosclerotic heart disease alone occurred with greater frequency in white patients than in those of the negro race. We believe that this is probably attributable to the fact that the average age of death in the negro race is much lower than in the white race, and, as a result, a smaller number of negroes reach that period of life in which this type of heart disease occurs.

A detailed discussion of all possible causative factors which might account for the much higher incidence of heart disease in the negro race will be presented in a future communication.

#### SUMMARY AND CONCLUSIONS

1. The incidence of organic heart disease in the Out-Patient Department of the John Sealy Hospital of Galveston, Texas is 3.3 per cent for all admissions and 16.3 per cent for those patients observed in the Medical Division.

2. Organic heart disease as seen in this clinic is of one and three-tenths times greater incidence in the male than in the female, and of one and seven-tenths times greater incidence in the negro than in the white race.

3. The hypertensive group (57.2 per cent), the arteriosclerotic group (20.2 per cent), and the syphilitic group (12.7 per cent) constitute 90 per cent of all cases of organic heart disease coming under observation.

4. Hypertensive heart disease, as seen in this dispensary, is of one and one-half times greater incidence in the female than in the male and is of two and one-half times greater incidence in the negro than in the white race.

5. Arteriosclerotic heart disease occurs three times as frequently in the male as in the female, and one and one-half times as frequently in the white as in the negro race.

6. Syphilitic heart disease is two and one-half times as prevalent in the male as in the female and of four times greater incidence in the negro than in the white race.

7. The incidence of rheumatic heart disease among all cases seen in the Medical Division is only 3.4 per cent.

8. The incidence of heart disease and particularly the relative incidence of the various etiological types in a community varies with the source of the material from which the data are compiled.

9. Attention is called to the much greater prevalence of heart disease in the negro race.

The writers wish to acknowledge their indebtedness to Dr. Joseph Kopecky who originally started the filing system which made this study possible.

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# THE LARGE Q-WAVE OF THE ELECTROCARDIOGRAM. A CORRELATION WITH PATHOLOGICAL OBSERVATIONS\*

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THE presence of a large Q-wave in Lead III has been noted by Pardee<sup>1, 2</sup> and Levine<sup>3</sup> in cases of coronary occlusion. Subsequent analysis of electrocardiograms at Montefiore Hospital confirmed their observations and also indicated that the large Q-wave was a frequent electrocardiographic sign in this condition. As the initial part of the QRS deflection† probably corresponds to the excitation of the septum and adjacent apices of the two ventricles (Lewis<sup>4</sup>), it appeared to us that damage to the septum with involvement of the minor conducting divisions supplying the apical regions, might be responsible for the production of the large Q-wave.

## THE FREQUENCY OF THE LARGE Q-WAVE

Before attempting a correlation with pathological material, the frequency of the large Q-wave was determined in the electrocardiograms of the last 140 cardiac patients at Montefiore Hospital. The records of the 35 necropsied cases considered in the correlation are excluded from this group. Pardee's criterion for a large Q-wave was adopted: that is, a negative wave of more than 25 per cent of the maximum deflection in whichever lead the latter occurred. In Pardee's collection of 227 records obtained from healthy adults with apparently normal hearts, only 2 presented a large Q-wave in Lead III.

Occasional difficulty was encountered in interpreting a small initial upward peak, especially in Lead III of left axis deviation records because of muscular tremors or oscillatory waves of auricular fibrillation. This difficulty was usually solved by scrutinizing all the complexes in the lead. Moreover, if the initial part of the QRS complex in Lead II was more negative than in Lead I, it was inferred that a doubtful preliminary deflection in Lead III was also negative.

Of the 140 patients with heart disease, 30 were clinically suspected of suffering from coronary artery disease; the records of 13 of these showed a large Q-wave in Lead III and another presented a large Q-wave in Lead II only. In this group of 30, 27 records showed left axis deviation. The electrocardiograms of the remaining 110 cases were classed according to axis deviation. None of the 30 with normal

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†Following Lewis' terminology, the Q-wave denotes an initial negative deflection of the QRS complex while the R-wave denotes an initial positive deflection.

axis deviation revealed a large Q-wave in any lead. In the 40 records with right axis deviation, a large Q-wave only in Lead III was observed in but 2, both being from children with congenital pulmonic

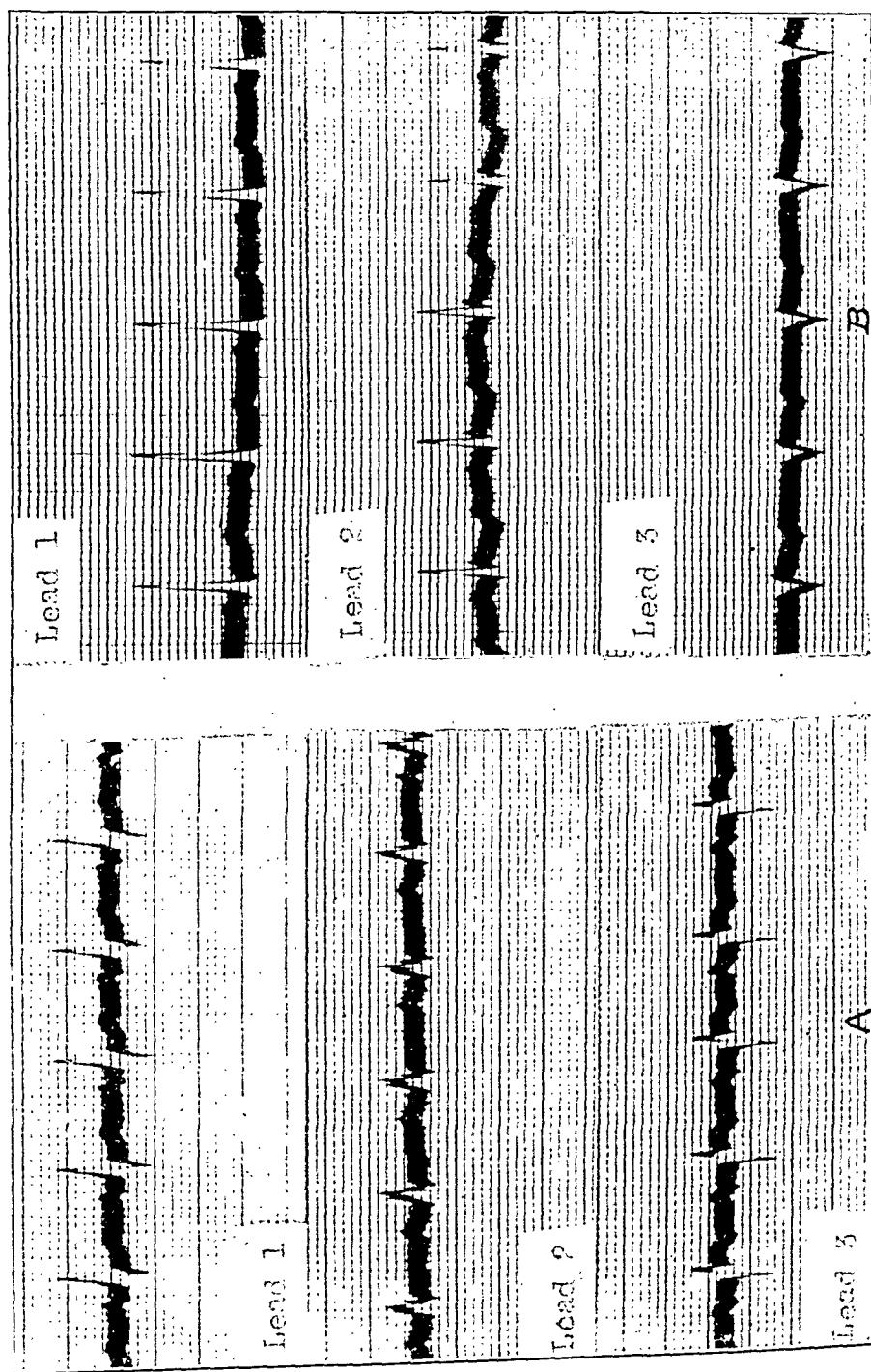


FIG. 1.—A, Case 6; B, Case 8. Both records show left axis deviation with a large Q<sub>3</sub>.

stenosis. Two of the 40 records of left axis deviation showed a large Q-wave in Lead III and one other showed a small Q-wave in Lead III. These 3 records were obtained from children with rheumatic mitral and aortic valvular lesions, aortic insufficiency predominating.



It is seen from these statistics that a large Q-wave in any lead of the electrocardiogram (excluding cases of congenital and advanced rheumatic heart disease) is unusual except in cases of myocardial involvement consequent upon coronary artery disease. Inasmuch as the great majority of records from cases suspected of myocardial infarction show left axis deviation, special attention is directed to the third lead in this type of record. In cases without myocardial infarction this lead usually shows a distinct initial upward peak or R-wave of considerably more than 5 per cent of the maximum QRS deflection before joining the principal downward deflection or S-wave (Fig. 3A). If the upward peak is less than 5 per cent of the maximum QRS deflection, the preliminary deflection cannot be classified (Fig. 3B). On the other hand, in the cases of myocardial infarction, this lead most frequently shows either a very large Q-wave due to the fusion of the initial downward deflection with the principal inverted deflection or no Q at all (Fig. 1).

#### CORRELATION OF ELECTROCARDIOGRAMS WITH PATHOLOGICAL MATERIAL

Thirty-five hearts from patients who died on the Medical Service during the past two years were then examined. The cases were not selected except for the exclusion of congenital and uncomplicated rheumatic hearts as well as those with records of major intraventricular conduction disturbance as differentiated by a QRS interval over .12 sec. In this particular type of electrocardiogram, there is represented probably a disturbance of conduction in either main branch, and minor aberrations in excitation cannot therefore be evaluated. Most of the patients suffered from hypertension, antecedent or persistent, with the chronic arteriosclerotic complications. The remainder of the series comprised 2 cases of syphilitic aortitis, 2 cases of polycythemia vera, and 2 cases of rheumatic carditis with concomitant hypertension. The majority were followed in the hospital for a few months and had several electrocardiograms taken. Successive electrocardiograms did not usually show much variation, since additional acute occlusions were infrequent. In correlating the records with the cardiac changes, due consideration was given to the lapse of time between the last record and the date of necropsy. The last record was taken within the month before death in all but 3 cases.

On gross examination the hearts were scrutinized particularly for the nature and site of myocardial damage with particular reference to interventricular septal involvement. Microscopical studies were made when gross inspection was inconclusive. In most of the cases, the myocardial damage consisted of healed infarcts or scattered patches of fibrosis resulting from occlusion of one or more of the principal coronary arteries.

In Table I are listed 12 cases with electrocardiograms of left axis deviation and a large  $Q_3$  (Fig. 1). Myocardial damage with involvement of the septum posteriorly, and in most instances anteriorly as well, was present in all the hearts. Case 12 showed a recent infarction of the posterior wall of the left ventricle and a recent thrombosis in the right coronary artery. Grossly the septum appeared normal and on microscopical examination only some small areas of fibrosis were seen. In the successive electrocardiograms of Case 12, a large  $Q_3$  was observed six months prior to death; this was absent three months later but reappeared five days before death from the acute coronary thrombosis. This case was also the only one demonstrating a transient large  $Q_3$ .

TABLE I  
LEFT AXIS DEVIATION WITH LARGE  $Q_3$ \*

| CASE NO. | PART OF SEPTUM INVOLVED                                      | INITIAL WAVE OF QRS |         |          | MAXIMUM QRS DEFLECTION |
|----------|--|---------------------|---------|----------|------------------------|
|          |  | LEAD I              | LEAD II | LEAD III |                        |
| 1        | Lower third, anteriorly and posteriorly                      | + 8                 | - 7     | -16      | 16                     |
| 2        | Lower posterior  | - 1                 | - 2     | -12      | 24                     |
| 3        | Lower half, anteriorly and posteriorly                       | - 1                 | - 2     | - 6      | 17                     |
| 4        | Diffuse fibrosis, especially posteriorly                     | - 1                 | - 0.5   | -13      | 14                     |
| 5        | Lower third, anteriorly and posteriorly                      | - 1                 | - 1     | - 6      | 15                     |
| 6        | Lower two-thirds, posteriorly                                | + 6                 | - 1     | - 5      | 7                      |
| 7        | Diffuse fibrosis of entire septum                            | + 5                 | - 2     | - 2.5    | 5                      |
| 8        | Lower two-thirds, posteriorly                                | +12                 | - 1     | - 4      | 12                     |
| 9        | Diffuse fibrosis of entire septum                            | +12                 | + 7     | -11      | 12                     |
| 10       | Lower half, anteriorly and posteriorly                       | +20                 | + 1     | -20      | 23                     |
| 11       | Diffuse fibrosis with necrosis in center beneath aortic ring | + 8                 | - 1     | -11      | 12                     |
| 12       | Slight fibrosis, especially posteriorly                      | - 5                 | - 1     | - 9      | 12                     |

\*All of these hearts showed healed myocardial infarcts or scattered areas of fibrosis subsequent to coronary artery occlusions. The extent of the septal involvement is given in the table. In the measurement of the initial wave of the QRS complex in each lead, the value of either the Q or the R is given in  $10^{-4}$  volts. The value of the maximum QRS deflection is taken from the lead in which it occurred, regardless of whether the deflection was upright or inverted.

Table II comprises 3 cases with tracings showing normal axis deviation and a large  $Q_3$  (Fig. 2A). In Case 14,  $Q_1$  was larger than  $Q_3$ . All three presented healed myocardial infarcts including the lower part of the septum anteriorly and posteriorly.

TABLE II  
NORMAL AXIS DEVIATION WITH LARGE  $Q_3$ †

| CASE NO. | PART OF SEPTUM INVOLVED                              | INITIAL WAVE OF QRS |         |          | MAXIMUM QRS |
|----------|--|---------------------|---------|----------|-------------|
|          |  | LEAD I              | LEAD II | LEAD III |             |
| 13       | Lower half, anteriorly and lower fourth, posteriorly | +5.5                | +8.5    | -3       | 8.5         |
| 14       | Lower third, anteriorly and posteriorly              | -3                  | -2      | -1       | 3           |
| 15       | Lower third, anteriorly and posteriorly              | -1                  | -1.5    | -2       | 4           |

†A healed myocardial infarct resulting from coronary artery occlusion was found in each of the three hearts.

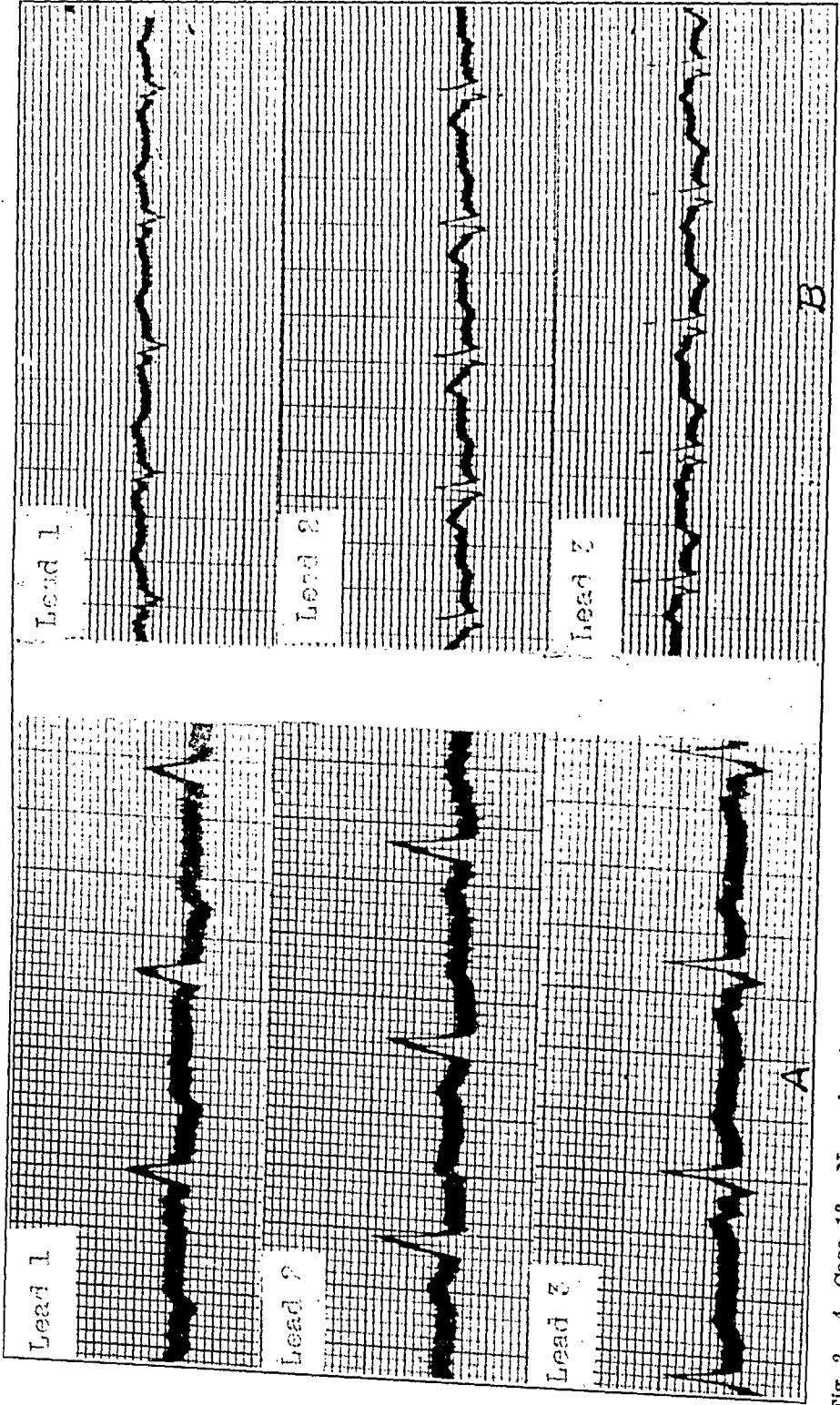


Fig. 2.—A, Case 13. Normal axis deviation with a large  $Q_1$ . QRS interval .11 sec. B, Case 16. Right axis deviation with a large  $Q_2$  and  $Q_3$ . QRS interval .11 sec.

In Table III are listed 2 cases with records of right axis deviation and a large  $Q_3$  (Fig. 2B). In Case 16,  $Q_2$  was slightly larger than  $Q_3$ . Myocardial damage with extensive involvement of the anterior and posterior portion of the septum was present in each heart.

TABLE III  
RIGHT AXIS DEVIATION WITH LARGE  $Q_3$ \*

| CASE NO. | PART OF SEPTUM INVOLVED                   | INITIAL WAVE OF QRS |         |          | MAXIMUM QRS |
|----------|---|---------------------|---------|----------|-------------|
|          |   | LEAD I              | LEAD II | LEAD III |             |
| 16       | Entire left ventricular surface of septum | +1                  | -2.2    | -2       | 6           |
| 17       | Lower half, anteriorly and posteriorly    | +5                  | +3      | -2       | 5           |

\*Both hearts showed myocardial scars and coronary artery closures.

Table IV contains 16 cases with records of left axis deviation and a positive preliminary deflection in Lead III of more than 5 per cent of the maximum deflection (Fig. 3A). In the first five cases (Cases 18 to 22) there was evidence of coronary occlusion and myocardial damage without any involvement of the septum. In the following 8 cases (Cases 23 to 30) the septum as well as the rest of the myocardium

TABLE IV  
LEFT AXIS DEVIATION WITH POSITIVE PRELIMINARY DEFLECTION IN LEAD III\*

| CASE NO. | PART OF SEPTUM INVOLVED        | INITIAL WAVE OF QRS |         |          | MAXIMUM QRS |
|----------|--------------------------------|---------------------|---------|----------|-------------|
|          |                                | LEAD I              | LEAD II | LEAD III |             |
| 18       | None                           | +14                 | +12     | +6       | 15          |
| 19       | None                           | -1                  | +7      | +2       | 9           |
| 20       | None                           | -2.5                | +9      | +7       | 14          |
| 21       | None                           | +0.5                | +1.5    | +2       | 14          |
| 22       | None                           | -1.5                | +3      | +5       | 27          |
| 23       | None                           | +8                  | +5      | +1.7     | 9           |
| 24       | None                           | -1                  | +1      | +2       | 23          |
| 25       | None                           | -1                  | +9      | +3.5     | 13          |
| 26       | None                           | +8                  | +3      | +1.5     | 9           |
| 27       | None                           | -1                  | +18     | +2       | 19          |
| 28       | None                           | -1                  | +3      | +2.5     | 20          |
| 29       | None                           | -1                  | +9      | +1.3     | 12          |
| 30       | None                           | +17                 | +13     | +2       | 17          |
| 31       | Extreme anterior margin        | +15                 | +3      | +2       | 16          |
| 32       | Lower third, anteriorly        | +7                  | +6      | +4       | 16          |
| 33       | Diffuse fibrosis of lower half | +6                  | +2      | +1.5     | 9           |

\*The hearts of Cases 18 to 22 revealed coronary occlusions and healed infarcts or fibrosis in the left ventricle without any septal involvement. In the heart of Case 23, an occlusion of a small branch of the left circumflex artery was seen, but the myocardium appeared normal. In the hearts of Cases 24 to 30, the myocardium was intact although there was slight to moderate sclerosis of the coronary vessels. The hearts of Cases 31 to 33 presented healed myocardial infarcts.

appeared intact. The last 3 cases (Cases 31 to 33) showed healed myocardial infarcts with septal involvement. Case 33 alone revealed damage in the posterior part of the septum.

In Table V are listed 2 cases with electrocardiograms of left axis deviation and unclassified preliminary deflection in Lead III. The

record of Case 34 contained a very small initial upward deflection in Lead III of only 4 per cent of the maximum deflection (Fig. 3B). In Case 35, the preliminary deflection in Lead III showed a pronounced

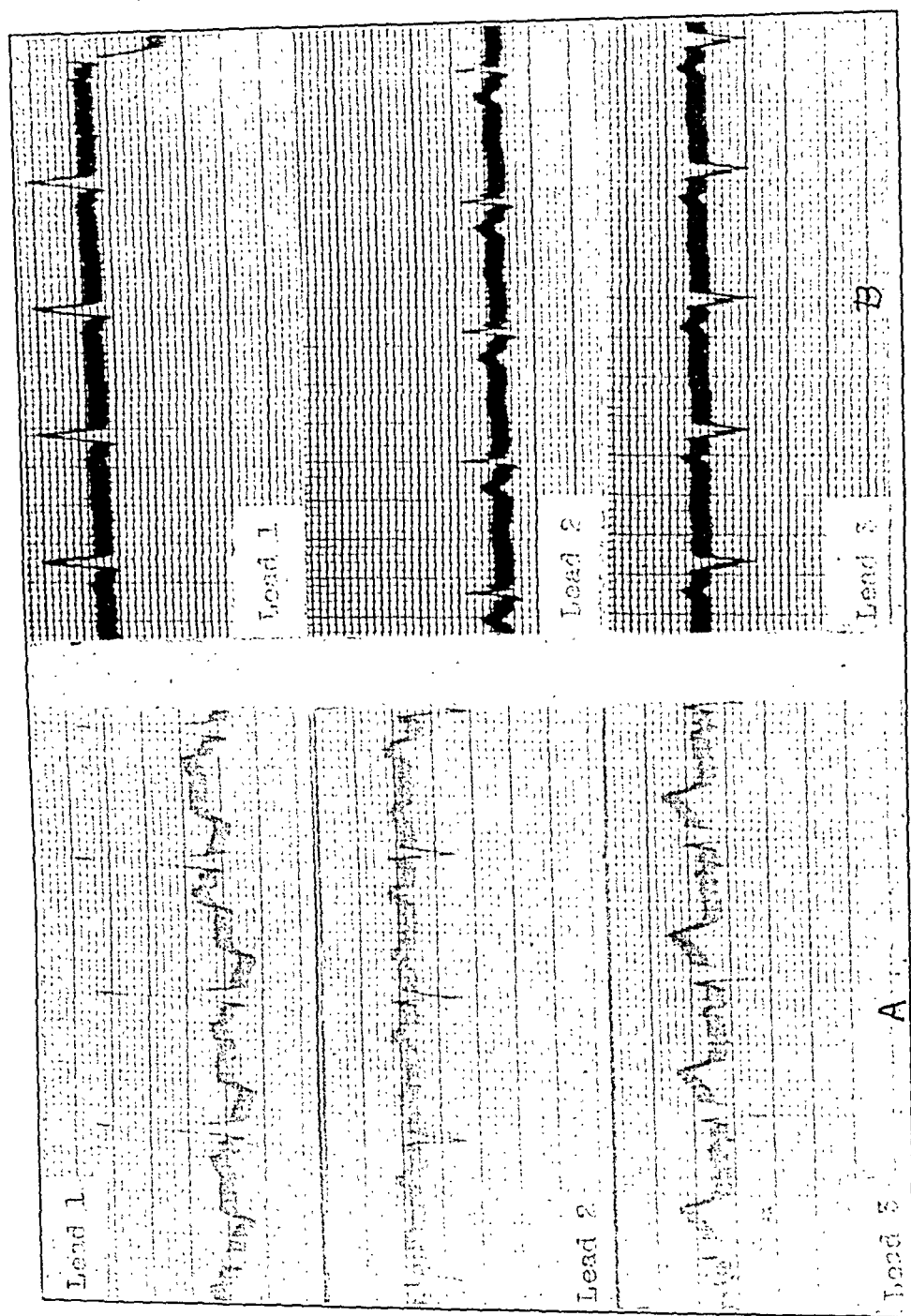


Fig. 3.—A, Case 24. Left axis deviation with a positive preliminary deflection in Lead III equivalent to 8 per cent of the maximum QRS deflection. This record represents the minimum ratio of  $R_2$  to maximum QRS in the entire group of Table III. B, Case 34. Left axis deviation with an unclassified preliminary deflection in Lead III.  $R_2$  is 4 per cent of the maximum QRS.

change during an intervening fifteen months' period, the second record having been taken one month before death. Although this last record did not present any  $Q_3$ , its preliminary deflection was definitely altered (Fig. 4). Healed myocardial infarcts with extensive septal involvement were present in both cases.

In consideration of the variability of the coronary circulation evident from the different sites of infarction with occlusion of the same

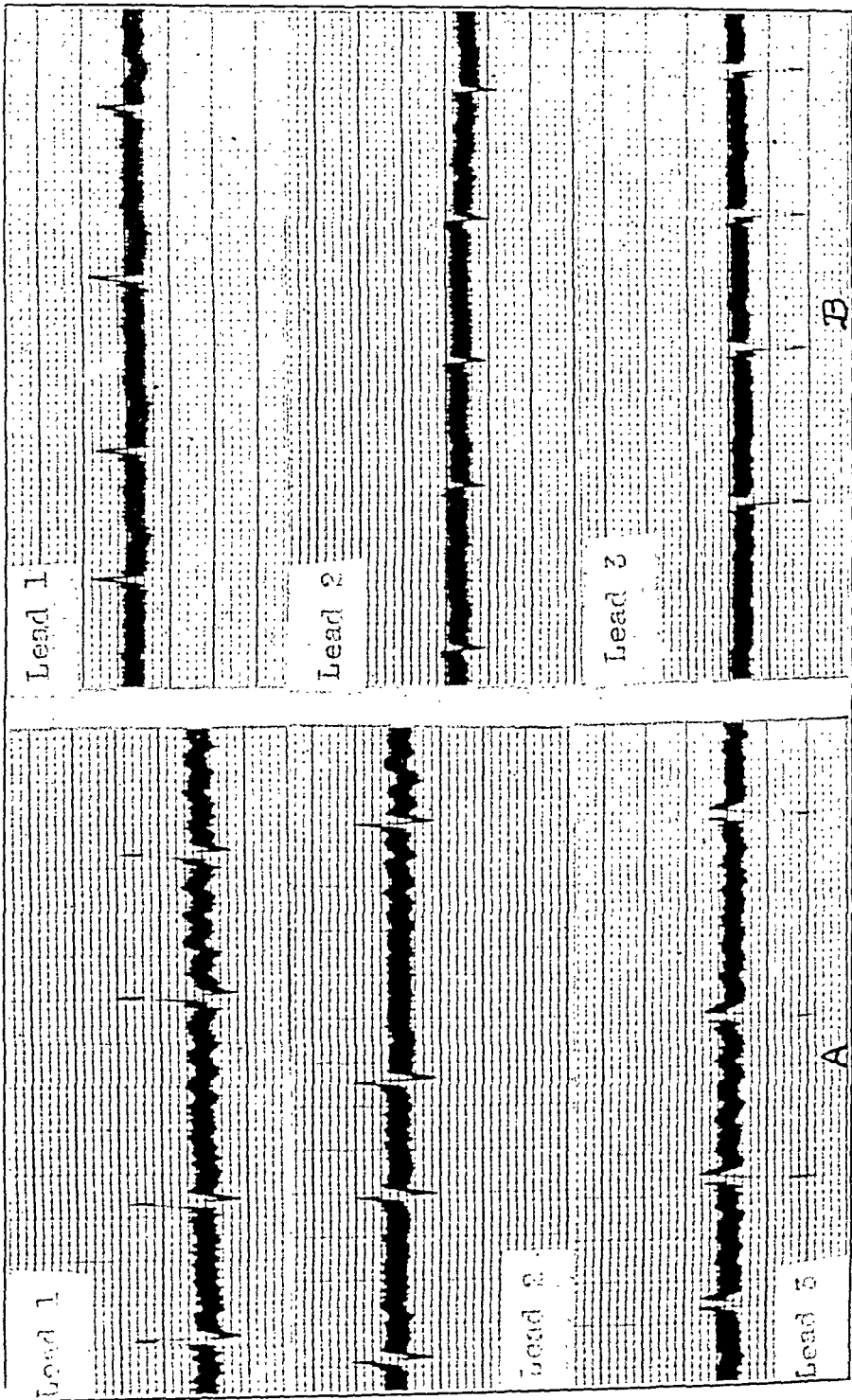


Fig. 4.—A, Case 35, sixteen months before death. Left axis deviation with a definite (20 per cent) preliminary R in Lead III that is partially obscured by the oscillatory waves of auricular fibrillation. B, the same case, one month before death. R<sub>1</sub> is smaller (12 per cent) and splintered.

vessels, and of a probable similar anatomical variability of the specialized conducting system, a more precise localization of the septal damage was not attempted. All of the 17 cases with a large Q<sub>2</sub> revealed septal involvement, at least in the posterior portion. In the

TABLE V

LEFT AXIS DEVIATION WITH UNCLASSIFIED PRELIMINARY DEFLECTION IN LEAD III\*

| CASE NO. | PART OF SEPTUM INVOLVED                | INITIAL WAVE OF QRS |         |          | MAXIMUM QRS |
|----------|--|---------------------|---------|----------|-------------|
|          |  | LEAD I              | LEAD II | LEAD III |             |
| 34       | Lower half, anteriorly and posteriorly | -0.8                | -1.4    | +0.3     | 8           |
| 35       | Lower half, anteriorly and posteriorly | -0.5                | +0.5    | +0.8     | 7           |

\*Both hearts showed coronary artery occlusions with healed infarcts.

16 cases without a large  $Q_3$ , only one showed involvement of the posterior portion of the septum. No attempt was made to correlate the pathology in the remaining 2 cases (Cases 34 and 35) with their unclassified electrocardiograms.

## COMMENT

These findings indicate that a large  $Q_3$  is associated with damage in the septum, particularly in the posterior portion. The frequency of the large  $Q_3$  probably depends on the proximity of the septum to the most frequent sites of infarction. The large  $Q_3$  ensues in the majority of instances when the resultant apical infarction, subsequent to occlusion of the left anterior descending branch, includes the lower posterior part of the septum. When the right coronary artery is occluded, the infarction in the posterior wall of the left ventricle usually involves the adjacent posterior part of the septum. The large  $Q_3$  was observed in 9 cases where the sole infarct occurred at the apex as well as in 4 cases where the sole infarct occurred in the superior or middle part of the posterior wall of the left ventricle. Accordingly, this excludes the possibility that the large  $Q_3$  is a consequence of one particular site of infarction in the walls of the left ventricle.

Six cases recorded a large  $Q_2$  which in 2 was even greater than the large  $Q_3$ ; while in another  $Q_1$  was the largest. Myocardial infarction with septal involvement was present in all 7. While these data are insufficient to draw any conclusions, it seems that a large  $Q_1$  or  $Q_2$ , normally infrequent, may have the same significance as the large  $Q_3$ .

The large  $Q_3$  is especially important because it is the most frequent electrocardiographic sign during the chronic period of myocardial infarction. Sometimes it is the only graphic clue to the pathological condition present in the heart. During the acute period of myocardial infarction, the large  $Q_3$  and the other characteristic signs commonly occur together; but in the period subsequent to the acute coronary thrombosis the R-T segment usually becomes iso-electric and the T-wave inversion becomes absent or limited to either Lead I or Lead III. This is borne out in our necropsied cases of myocardial infarction or fibrosis, predominantly of chronic nature; a large  $Q_3$  is present in 17, whereas a negative T in at least two leads is found in 8, and an abnormal R-T segment in 6. Electrocardiograms with QRS intervals

over .12 sec., such as occur in bundle-branch block or arborization block, were not included in this study. Although such records are also indicative of coronary artery disease, they are not seen as often as those with normal QRS intervals.

An inspection of the cases of coronary thrombosis reported by others presents some similar findings. On examining the 82 electrocardiograms of Levine's<sup>3</sup> series, a large  $Q_s$  is found in approximately 40 per cent, including the 4 cases where definite mention is made of septal infarction. In Barnes and Whitten's<sup>5</sup> series, there is no instance where a large  $Q_s$  occurs without septal involvement. However, in 3 cases in which involvement of only the anterior part of the septum is described, no abnormal  $Q_s$  is seen. The findings in the last 3 cases thus correspond to our observations in Case 31 and Case 32.

Some of the electrocardiograms of Levine's series, taken shortly after an acute occlusion, showed a large  $Q_s$  which subsequently disappeared. A transient large  $Q_s$  was present in only one of our cases (Case 12) probably because our patients were not usually observed in the period immediately following the acute thrombosis. Temporary circulatory disturbance of that part of the septum adjacent to an area of infarction may be responsible for the production of a large  $Q_s$  which later disappears, possibly due to the development of a compensatory collateral circulation. Consequently, a transient large  $Q_s$  may also be considered as indicative of myocardial involvement. Pardee<sup>2</sup> observed a transient large  $Q_s$  in the records of a boy during a bout of acute rheumatic carditis. This may have been due to an acute inflammatory lesion in the septum.

It is interesting to note that the experimental work in dogs yields some suggestive observations. Rothberger and Winterberg<sup>6</sup> studied the electrocardiographic changes following severance of the anterior and posterior divisions of the left bundle-branch. When either division was cut, no widening of the QRS complex occurred. After cutting the posterior primary division, they noticed a prominent increase of the R in the ano-esophageal lead. In their observations they did not include any comparatively small alterations in the early part of the QRS complex. However, on comparing their records from four experiments in which the posterior division was divided, a small Q which is absent in the ano-esophageal lead of the control records, is seen in the ano-esophageal lead of three of the four postoperative records. Otto's<sup>7</sup> records also demonstrate the appearance of a small Q in the axial lead (Lead II) after section of the posterior division. Although a large Q was not recorded following these operations, nevertheless the change from a preliminary upward to a small downward deflection may possibly be sequential to a similar aberration of ventricular excitation in the dog.



## THEORETICAL CONSIDERATIONS

Before considering the origin of the large  $Q_3$ , it is necessary to investigate the influence of ventricular hypertrophy and heart position upon the deflections occurring during the various periods of ventricular activation. Lewis<sup>4</sup> concluded that the inscription of Q and the beginning of R corresponded in time to the excitation of the septum, right papillary muscle, apices of the two ventricles and immediately adjoining areas; the most prominent part of R, he ascribed to activation of the mass in the walls; and the last part of the QRS complex, predominantly to basilar excitation. While these conclusions were deduced from experimental work in dogs, they are probably even more applicable to man. Because of the relatively larger dimensions of the endocardial surfaces of the human ventricles, a greater proportion of time is required to distribute the excitation wave to the various endocardial regions. Therefore, the septum, adjacent anterior and

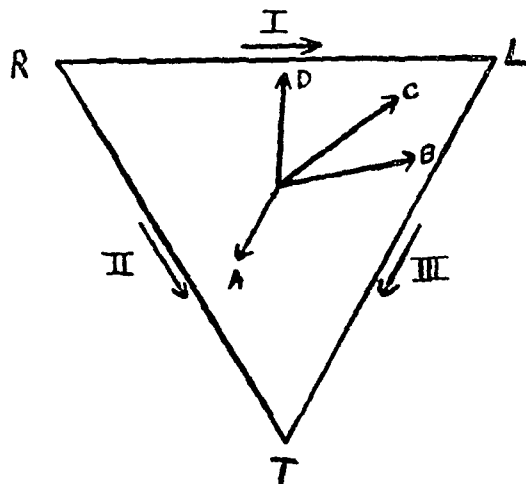


Fig. 5.—The electrical axes calculated from four electrocardiograms at .02 sec. and drawn to the same scale. A from Fig. 3A; left axis deviation with a preliminary R. B from a record of right axis deviation with a small  $Q_3$ . C from Fig. 1A; left axis deviation with a large  $Q_3$ . D from Fig. 2B; right axis deviation with a large  $Q_2$  and  $Q_3$ .

R, L, and T represent respectively, the right arm, left arm, and left leg electrodes. The arrows indicate the directions associated with positive deflections in the three leads.

posterior walls, and adjacent apices of the two ventricles, being nearest to the bundle branches, would most likely be activated first. The anterior and posterior walls, by producing potential differences during activation that lie perpendicular to the frontal plane of the three electrodes, hardly affect the standard electrocardiogram and their influence may consequently be disregarded.

In the electrocardiograms of left axis deviation from cases uncomplicated by myocardial damage, the preliminary deflection is usually opposite to the main deflection, so that a small Q is most often present in Lead I and a small R in Lead III. In hearts with this type of record, the septum and adjacent inferior portions of both ventricles are

frequently displaced to the right by the relatively greater left ventricular hypertrophy. This is best seen *in situ* at post-mortem examination of cases with cardiac hypertrophy secondary to hypertension. The displacement of these regions, first activated, thus corresponds, in general, to the direction of the early electrical axes which are inclined downward and to the right as calculated from the initial negative deflection in Lead I and positive deflection in Lead III (Fig. 5A).

If one excludes cases of myocardial infarction, right axis deviation electrocardiograms usually show a positive preliminary deflection in Lead I and a small Q in Lead III, both being in opposite phase to the principal deflection. In these cases the relatively greater right ventricular hypertrophy causes a displacement of the septum and adjacent inferior portions upward and to the left, and the heart often rotates around its long axis so that the left ventricle lies more posteriorly, with the right ventricle forming almost the entire anterior cardiac surface. In advanced mitral stenosis this alteration of relations is particularly noticeable. The rotation and displacement of the septum and adjoining apical regions upward and to the left thus approximately corresponds to the direction of the early electrical axes calculated from the positive deflection in Lead I and the negative deflection in Lead III (Fig. 5B). This alteration, particularly marked on post-mortem examination of several hearts with congenital pulmonic stenosis, may explain the large  $Q_3$  recorded in their electrocardiograms. In children and young adults with advanced rheumatic mitral and aortic lesions producing hypertrophy of both chambers, a similar displacement of the lower part of the septum is frequently present. However, some of these cases record electrocardiograms of left axis deviation due probably to the later excitatory preponderance of the lateral wall of the left ventricle. Hence the large  $Q_3$ , recorded in advanced rheumatic heart disease, may be due to considerable septal displacement and therefore does not necessarily indicate any aberration in ventricular excitation such as occurs with myocardial infarction.

Pardee<sup>2</sup> observed that a large  $Q_3$  occasionally ensues from the displacement of the heart upward and to the left because of elevation of the diaphragm during deep expiration and at times even during pregnancy. Rotation of the early and later electrical axes upward and to the left occurs and is sometimes represented by the large  $Q_3$ . The alteration of the deflections with respiration is usually most marked in Lead III, for the electrical axes are most frequently directed approximately perpendicular to the line of this lead and consequently their projections on this line, representing the Lead III deflections, show the greatest variation. Einthoven<sup>5</sup> was the first to explain this phenomenon. The influence of deep expiration must therefore be considered before interpreting electrocardiograms with a large  $Q_3$ .

Our interpretation of the presence of a large  $Q_3$  secondary to myocardial infarction is based on a minor aberration in ventricular activation. Assuming that the septum is so injured that the descending divisions to the left apex are principally involved, then the downward directed potential differences ordinarily generated by excitation at the medial part of the left apex are no longer recorded during the early period of the QRS deflection. Accordingly, the remaining upward directed potential differences in this period are no longer neutralized, and the electrical axes of the early intervals incline more definitely upward and with greater potential values. This is represented in the electrocardiogram by a prominent early negative deflection in the two semivertical leads (Leads II and III) (Fig. 5D). Because of the rich intraventricular anastomoses of the so-called Purkinje network, the excitation of the apex is only slightly delayed. Pronounced widening of the QRS interval is not produced, for, despite this delay, the excitation of the apex probably occurs within the time required for complete excitation of the more distant basilar portions of the ventricles.

The above explanation pertains to the large  $Q_2$  or  $Q_3$  recorded in the electrocardiogram with any type of axis deviation. Left axis deviation records of myocardial infarction, in particular, frequently present in Lead III a very large Q due to the fusion of the negative initial deflection with the negative main deflection. In such instances, the activation of the hypertrophied left ventricular musculature produces greater potential differences directed upward and toward the left, especially during the later intervals. Hence both early and later axes incline upward as well as to the left and lie approximately parallel to the line of Lead III. With the electrical axes lying in this direction,  $Q_3$  is the larger, although  $Q_2$  is usually also present ( $Q_2$  is present in 10 of our 12 records of left axis deviation with a large  $Q_3$ ) (Fig. 5C).

The investigation of our pathological material and the slight evidence from the experimental work in dogs suggest that injury to the smaller divisions in the posterior portion of the septum is particularly responsible for the development of this characteristic Q-wave. It is possible that the anterior subdivisions supply principally the anterior walls where activation does not affect the standard electrocardiogram significantly.

#### SUMMARY

(1) The frequency of the large Q-wave was investigated in the electrocardiograms of 140 patients with various types of heart disease. A large  $Q_3$  was observed in the records obtained from 13 patients suspected of coronary artery disease, 3 patients with advanced rheumatic heart disease, and 2 patients with congenital pulmonic stenosis.

(2) The records of an additional group of 35 cases which came to necropsy were examined and a large  $Q_3$  was found in 17 of the 27 cases with evidence of myocardial infarction or fibrosis; in the remaining 8 cases in which there was no myocardial damage, none recorded a large  $Q_3$ .

(3) A correlation of the electrocardiograms with the pathological findings indicates that:

a) The large  $Q_3$  is the most frequent electrocardiographic sign of coronary artery disease during the chronic period.

b) The large  $Q_3$  in myocardial infarction or fibrosis is probably due to involvement of the septum, particularly in its posterior portion.

(4) A theoretical interpretation of the production of the large  $Q$  is presented.

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# THE NATURE OF EXPERIMENTAL FLUTTER AND FIBRILLATION OF THE HEART\*†

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## ARGUMENT

SEVERAL theories have been advanced to explain auricular and ventricular fibrillation. One of the earliest to be proposed was by Kronecker<sup>1</sup> who suggested the existence of a coördinating center in the interventricular septum of the heart. Puncture of this center was supposed to be followed by incoördination of myocardial contraction, manifested as fibrillation. MacWilliam<sup>2</sup> showed that it was unnecessary to assume the existence of such a center because he could produce fibrillation in an excised mass of muscle taken from a place at some distance from the supposed location of the center. MacWilliam suggested instead that fibrillation was due to a disturbed relation between the refractory phase, which was shortened, and conduction time, which was prolonged. The contraction wave in passing through the muscle mass thus encountered some muscle bundles which had recovered before the others. These contracted earlier and resulted in incoördinated myocardial activity. A somewhat similar theory was proposed by Winterberg<sup>3</sup> who suggested that fibrillation was due to multiple foci, causing numerous simultaneous or nearly simultaneous local contractions and that these prevented a coördinated contraction of the chamber of the heart as a whole. This theory was subjected to experimental analysis by Rothberger and Winterberg<sup>4</sup> who recorded simultaneously the local electrical and mechanical oscillations from two widely separated points of the fibrillating ventricle. It was found that these oscillations, from two different points, were rhythmic for short periods in some of the records. Such a relationship is difficult to correlate with activity due to multiple foci acting independently at the same time and Rothberger and Winterberg<sup>4, 5</sup> then proposed a modification of the theory. The modified theory supposes that both flutter and fibrillation are forms of tachysystole due to impulses from one or more ectopic foci. It is emphasized that one such ectopic focus may be sufficient to produce this phenomenon. The gross appearance of a fibrillating or fluttering chamber is due to the great rapidity of

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contraction which results in feeble individual contractions. The great increase in rate of contraction is made possible in part by vagus activity, resulting in a shortening of the refractory phase. It is possible, experimentally, to increase the rate in fibrillation three- or fourfold by vagus stimulation, Samojloff.<sup>6</sup> Hering<sup>7</sup> and Haberlandt<sup>8</sup> suggest that fibrillation is due to rapid stimuli issuing from the A-V node rather than from one or more ectopic foci anywhere in the auricles or ventricles, and Scherf<sup>9</sup> assumes that the sinus node may play a similar rôle.

The foregoing conception that fibrillation is a form of tachysystole or coördinated rapid contraction of the entire chamber is challenged by Garrey<sup>10</sup> on the basis that the excitability is too low and the refractory period, shortened as it may be experimentally, is still too long to permit such rapid coördinated contractions. A more serious objection pointed out by Garrey<sup>10</sup> was that fibrillation stopped in a narrow strip of muscle cut out of a large fibrillating mass even if the strip were left attached at both ends to the main mass of fibrillating tissue. This experiment is a strong argument against fibrillation being a coördinated contraction of an entire chamber. It is particularly contradictory to the assumption that the tachysystole is due to a single activating focus, because slower waves were seen to pass along this bridge of muscle at times in one direction and at other times in a different direction.

In contrast to the foregoing is the widely accepted "circus theory" as developed by Lewis and his coworkers and based on previous work reported by several observers. Mayer,<sup>11</sup> in 1908, excised a ring of tissue from the bell of the large Medusa Cassipeia and by producing temporary block in one region caused a contraction wave to circulate around this ring. Mines,<sup>12</sup> in 1913, cut a ring of muscle from the heart of a tortoise, including auricle and ventricle. He produced a circulating wave in this specimen and noted that a shortened refractory phase and prolonged conduction time were necessary factors in the production of such a circus mechanism. He suggested at that time that such a circus wave may be responsible for paroxysmal tachycardia and fibrillation of the heart. He also demonstrated circus movement in the auricles of large rays and reported having observed such a preparation in which the circulating wave completed about fifty revolutions. Garrey<sup>13</sup> cut a wide ring of tissue from the fibrillating ventricle of a marine loggerhead turtle and observed that this wide ring continued to fibrillate. By cutting this fibrillating ring so as to make it narrower, fibrillation gave way to a circulating movement which Garrey called "circus motion."

The further development of the circus theory of fibrillation was then undertaken by Lewis and his coworkers and they have offered much experimental evidence as proof of the assumption that flutter

and fibrillation are due to a single, rapidly circulating, mother wave giving off centrifugal waves to the remainder of the chambers involved.

Lewis, Feil and Stroud<sup>14</sup> induced experimental auricular flutter in animals and recorded the electrocardiographic phenomena by direct leads from the auricles. They determined that the direction of the excitation wave was independent of the point of electrical stimulation. They traced the course of the excitation wave in flutter and established its path over the surface of the right auricle and the exposed portion of the left. The remainder of the path was calculated.

In a later publication Lewis<sup>15</sup> describes the underlying mechanism as a single circulating central or mother wave which traverses the same path constantly and which sends out centrifugal waves to the auricular musculature not in contact with the mother wave. Impure flutter and auricular fibrillation are stated to be due to the same mechanism, except that the single, central mother wave and centrifugal waves are deviated from the original paths by local areas of block or areas of partial refractory state not yet completely recovered. It is emphasized that there is only one central or mother wave in auricular fibrillation (Lewis<sup>16</sup>) whose location is usually such as to encircle the superior and inferior vena cava, regardless of the point at which the electrical stimulus was applied.

Lewis, Drury and Iliescu<sup>17</sup> studied clinical flutter in man by applying chest leads in three different planes. The rotation of the electrical axis with each auricular cycle was thus calculated and found to be  $360^\circ$  in the three planes, thus apparently substantiating the experimental conclusions previously quoted.

De Boer,<sup>18</sup> working with frogs' hearts, experimented with ventricular fibrillation after bleeding the animals. He, too, believes that the underlying mechanism is a circulating excitation wave passing through the cardiac muscles in stages.

The conception that a single mother circulating wave, usually located about the orifices of the two venae cavae is responsible for auricular fibrillation is open to criticism. Rothberger<sup>5</sup> points out that Lewis actually demonstrated *an almost complete circus path in the auricle of only one animal*. Calculations were substituted in the other experiments for those portions of the path which could not be actually demonstrated. He further points out that the taenia terminalis is not in itself a closed anatomical ring, hence the wave of excitation must leave it and then return to it in order to complete the circuit. The circus path is admittedly not along an anatomically distinct tract nor has block been demonstrated to exist to confine the path to such a ring. This is proved by the fact that centrifugal waves pass from the central mother wave to the rest of the auricular musculature. It is difficult to understand why the mother path should remain so con-

finer to one ring-like area. Areas of partial refractoriness or of block are admitted to exist in the path of the central wave in auricular fibrillation, causing this central wave to assume a sinuous path. But why should the impulse always return to the same point of origin? In the case of clinical flutter where the axis rotation was calculated to be  $360^\circ$  with each auricular cycle an objection may be raised that the electrocardiographic tracings from the chest leads probably included the effects from the centrifugal waves as well as from the comparatively narrow central wave. The results would then represent factors other than those from the narrow single central wave. Our experiments with direct leads, to be described later, showed that impulses other than from the auricle may also be registered.

Experiments performed by Scherf<sup>9</sup> raise further difficulties. This observer produced experimental flutter in dogs and then crushed the site where the central wave usually circulates. Electrocardiograms taken after such crushing of the central circulating wave should produce changes in the electrocardiogram, but no such change occurred in 16 of 17 experiments. It is possible, but not probable, that the path of the central wave was not included in the area crushed, hence the theory of Lewis is not altogether disproved by these experiments.

The explanation of fibrillation as proposed by Garrey<sup>10</sup> differs radically from any of the foregoing theories. This author believes that an impulse spreads in all directions in the auricles but that it may be limited or deflected by local areas of transient or permanent block. Relative differences between excitability and conductivity in an area may act like areas of block. The areas of block may shift in location at times or remain or recur at the same points. Such areas of obstruction would cause the impulse to assume circuitous paths and would act to break up the initial single impulse into several "daughter" impulses, each shuttling and weaving about among the areas of block. An area partly enclosed or protected by block from the stimulus at one instant may respond when an impulse reaches it from another direction or after the block has passed. Such an area may then become a center from which further impulses may shuttle about simultaneously and a circus movement obtains when the impulse happens to return to the point of origin. Such a return is not constant nor is it a fundamental factor in the mechanism, in the sense advocated by Lewis.

Our experiments were planned to test the validity of certain features embodied in the various theories of fibrillation. We have seen that the existence of a single focus or a single mother ring which feeds impulses to the remainder of the auricle are important features of two of the more widely accepted theories. It is true that Rothberger states that one or several foci may be responsible for the tachysystole which



he regards as the mechanism of fibrillations; still he leaves the impression that he leans to the idea that one focus is the more likely cause.<sup>19</sup>

Nearly all authors, including Lewis, believe that the underlying mechanism of auricular and ventricular fibrillation is the same. Our first undertaking was to determine whether one focus or one mother ring is the cause of fibrillation. We began working with ventricular fibrillation in the dog because it was easy to induce and because it was permanent. If it is true that one focus or one mother ring is responsible for the mechanism, then complete separation of the two ventricles should result in disappearance of fibrillation from one chamber or at least in very great modification of the electrocardiogram as it appeared in the control taken before the separation of the ventricles.

#### RESULTS

*Ventricular Fibrillation.*—In order to determine this point, dogs were used under morphine-sodium barbitol anesthesia and artificial respiration. The thorax was widely opened in order to expose the heart. The pericardium was opened longitudinally and its margins were fixed to the chest wall on either side to form a cradle on which the exposed heart rested. Two direct leads from nonpolarizable boot electrodes were fastened to each ventricle and control tracings were taken. Ventricular fibrillation was induced by a very short faradic stimulation of the base of the right ventricle and a sufficient length of time, usually about one minute, was allowed to pass in order to be certain that the fibrillation which was grossly apparent was permanent and spontaneous. Control tracings of each ventricle were taken in turn when the fibrillating contractions had visibly reached a more or less constant rate. The ventricles were then very quickly severed from one another along the interventricular septum and in most instances the entire heart, including the auricles, was cut completely across. It was important to work very quickly and to be certain that the two fragments were in the same relative position on the pericardial cradle as before the separation, in order to prevent artefacts due to natural slowing of the fibrillation rate or to change in position of the fragments. Electrograms were then taken of each ventricle in turn, after these foregoing precautions were carried out.

It was apparent on gross inspection that both ventricles continued to fibrillate in about the same manner as before separation. This fibrillation was grossly visible for several minutes. Comparison of the electrograms from both ventricles before and after separation in twelve experiments showed practically no change aside from a slowing in rate (Fig. 1). The results of these experiments lead us to conclude that a single mother ring or a single focus cannot be responsible for the mechanism of ventricular fibrillation in both ventricles. As a

further check, an experiment was performed in which simultaneous electrograms of the two ventricles were recorded (Fig. 2). The persistence of the fibrillation in the separated ventricles is clearly shown, as is the gradual slowing in the two sides.

*Auricular Fibrillation.*—We then embodied a similar principle in experiments designed to test the possibility that a single mother ring or a single focus is responsible for auricular flutter and fibrillation. Dogs prepared in the same way as before were used. The direct leads

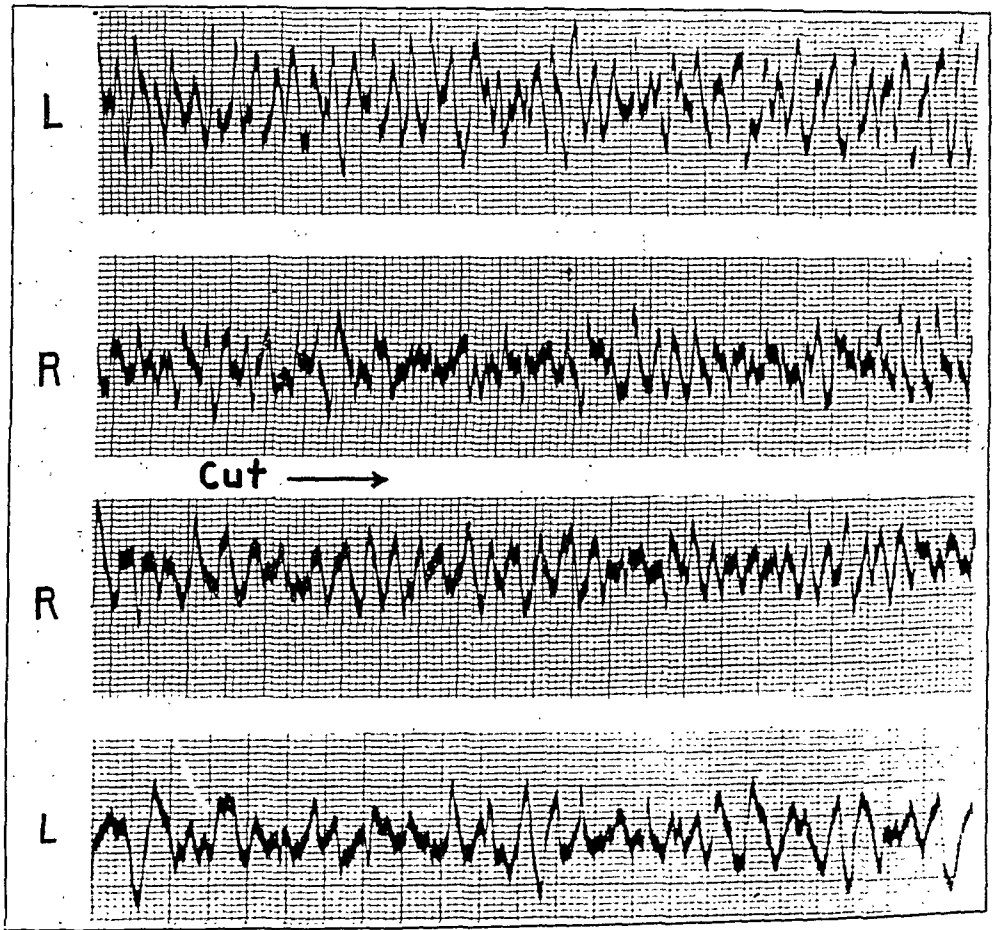


Fig. 1.—Electrograms from right (R) and left (L) ventricles showing persistence of ventricular fibrillation after complete separation of two ventricles by cut. Note in particular the approximate constancy of the two curves of the right ventricle taken before and after the cut.

from the appendices of each auricle were made with nonpolarizable boot electrodes. In the early records one electrocardiograph was used and the records from the auricles were obtained alternately. Later two electrocardiographs were used, each connected with one of the direct leads of an auricle, and simultaneous tracings were taken of both sides. Auricular flutter and fibrillation were induced by short faradic stimulation, of variable frequency and strength, applied to the right auricle, usually just above the inferior vena cava. As is well known, prolonged auricular fibrillation in the dog is not easy to induce. Numer-

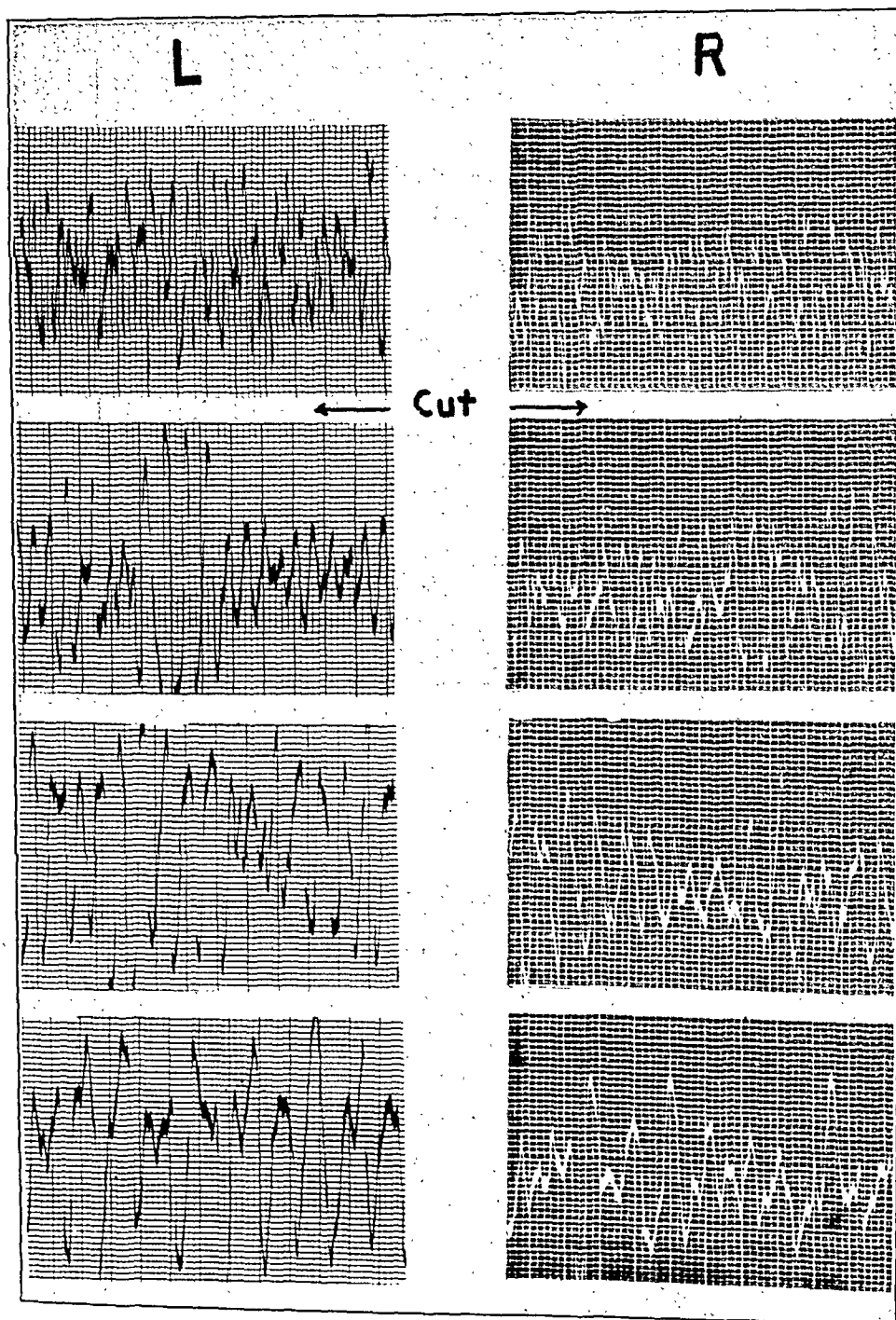


Fig. 2.—Simultaneous electrograms from right (R) and left (L) ventricles showing persistence of ventricular fibrillation after complete separation of two ventricles by cut. Note the simultaneous and progressive slowing of the rate of oscillation in the two ventricles.

ous animals were used and no further manipulations were made until the auricles were visibly fibrillating spontaneously at least twenty-five seconds after the faradic stimulus was removed. A crushing clamp was then applied between both auricles, while fibrillation or flutter still persisted and electrograms were taken from each auricle for some time.

In the early records, such as shown in Fig. 3, the fibrillation of the auricles persisted after the crush, the rate of the *f*-waves being the same as before the crush although their contour is altered slightly. The difference in rate of the *f*-waves on the two sides also persisted after the crush.

Before proceeding with the actual analysis of the later electrograms obtained simultaneously from direct leads from both auricles, it will

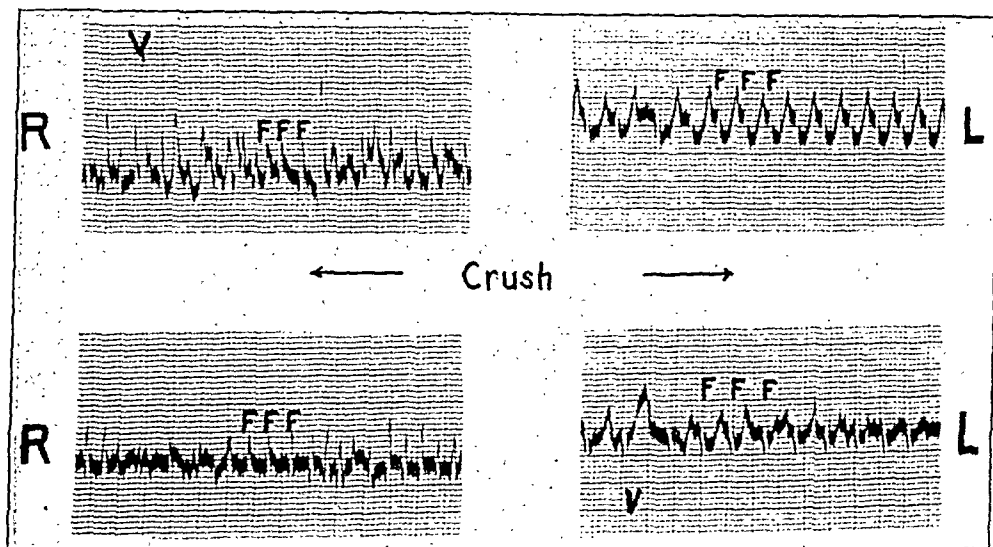


Fig. 3.—Electrograms from right (R) and left (L) auricles showing persistence of impure flutter after complete separation of two auricles by crush. V, deflection caused by ventricle; F, impure flutter waves. Note the difference in the rate of the flutter waves on the two sides which persists after crush.

be necessary to discuss certain possible artefacts and sources of error due to misinterpretation of the resulting curves.

The first of these is the possibility that the clamp did not reach clear across the auricles. The impulse from the right auricle could then reach the left by pursuing a circuitous course in the auricular tissue extending beyond the tips of the forceps. Such a technical error was prevented by applying the forceps from above toward the ventricles and by examining the position of both blades immediately after clamping and after the experiment was finished. We thus assured ourselves that both blades of the forceps extended not only completely across the interauricular region but also included a large part or all of the ventricles both on the dorsal and ventral aspects of the heart.

There was a further possibility that our crushing forceps were not strong enough to cause complete functional separation of the two

auricles. This was guarded against by using a large, heavy crushing forceps with long blades, such as is used by surgeons to crush bleeding thyroid tissue *en masse*. Examination of the crushed region after removal of the clamps showed distinct tissue destruction, at times resulting in profuse hemorrhage from perforation when the forceps were removed. Gross inspection of the auricles after application of the clamp showed incoördination of rhythm of the two auricles, one chamber beating at a different rate from the other or one auricle continuing to beat while the other was inactive. Electrographic evidence of such dissociation is seen in Fig. 5 in which simultaneous electrograms taken from both auricles shows marked asynchronism and differences in rate.

It was also necessary to consider the possibility that the severe trauma caused by crushing could by itself induce auricular flutter or fibrillation and that the site of injury could then act as a focus from

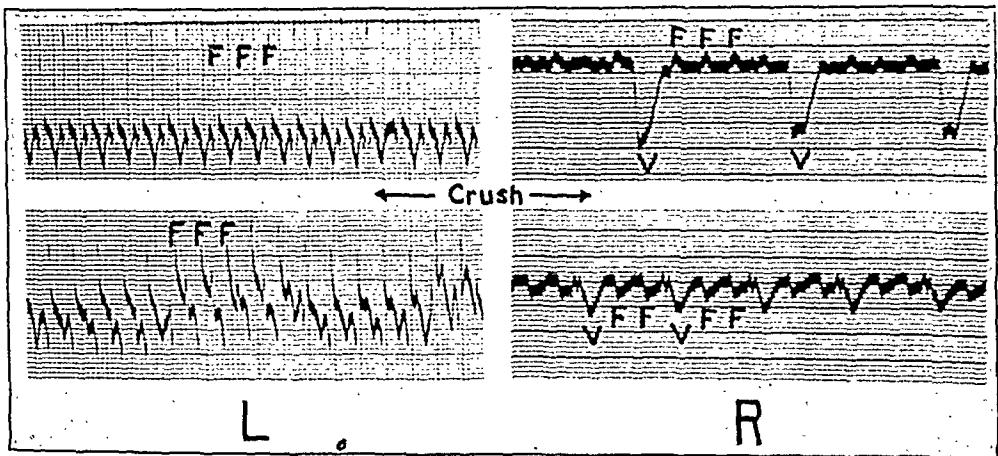


Fig. 4.—Simultaneous electrograms from right (*R*) and left (*L*) auricles showing persistence of impure flutter after complete separation of two auricles by crush. The string of the electrocardiograph recording the curve from the left is much more sensitive than that from the right.

which impulses could flow to both auricles. We tried many times to produce flutter or fibrillation by clamping and crushing various parts of both auricles during sinus rhythm but were consistently unsuccessful. In fact, all activity, both regular rhythm and fibrillation, would cease if the portion clamped off were small enough. This change was also corroborated electrocardiographically.

In the analysis of the electrograms it was necessary to bear in mind that the various complexes obtained from direct leads to the auricle would differ greatly from the corresponding complexes obtained with indirect leads from the extremities. It was necessary to determine how much the ventricles contributed to the electrograms taken directly from the auricles. Such a precaution is very important as previously pointed out in discussing the work of Lewis, both in the experimental animal and in his calculations in human auricular flutter. Direct leads from each auricle were therefore taken simultaneously with an

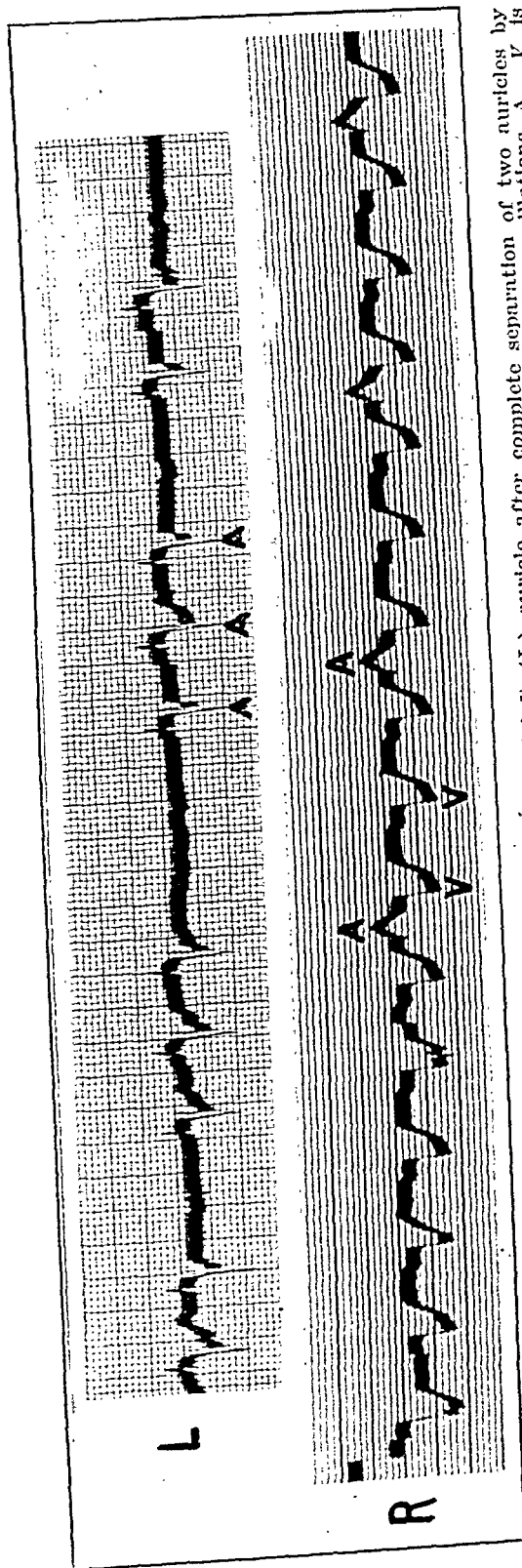


Fig. 5.—Simultaneous electrograms obtained from right (R) and left (L) auricle after complete separation of two auricles by crush and after impure flutter had stopped, showing independent rhythms of the two auricles indicated by oscillations A. V is deflection from ventricles.

indirect lead (Lead II). It was found by comparing the curves from such simultaneous direct and indirect leads that the ventricles often produced distinct deflections in the record of the direct leads of the auricles. This was shown when stimulation of the left vagus produced partial A-V block with dropped ventricular complexes, thus clearly separating the ventricular from the auricular complexes.

Heart-block was produced before starting the experiment in order clearly to distinguish the *f*-waves of the induced flutter and fibrillation from components due to the ventricles. For this purpose the region of the bundle of His was crushed. We found that this procedure produced a temporary marked slowing of the ventricle. The ventricular rate then gradually became more rapid. The crush tended to exaggerate the ventricular complexes and make them monophasic so that they were more easily distinguishable.

The curves of Fig. 4 show the simultaneous records of the two auricles in such an experiment after the fibrillation had been induced. In the electrogram from the right auricle (segment on right) the large monophasic ventricular complexes can be recognized; they occur regularly at a rate of 50 per minute. The smaller monophasic *f*-waves occurring at the rate of about 300 per minute can also be readily seen. The electrogram from the left auricle, in which the string was more sensitive than the right, shows no evidence of the ventricular activity. The large deflections are the *f*-waves which correspond in rate to those on the right side.

The lower curves show the simultaneous records obtained after a complete separation of the two auricles by use of the crushing clamp. The ventricular deflections seen in the record on the lower right are smaller and faster in rate, the *f*-waves have not changed in rate but have a different contour probably because of the new injury currents. The contour of the *f*-waves in the left auricle has also been altered for a similar reason.

We are forced to conclude, therefore, that the rapid oscillations in both electrograms, representing *f*-waves of impure auricular flutter, persist after crushing. We came to the same conclusion in seven other experiments conducted in the same manner except that the bundle of His was not always crushed before fibrillation or flutter was induced.

If a single focus or single mother ring, located in an auricle, be responsible for auricular flutter and fibrillation in the intact heart, then functional separation of the two auricles should result in cessation of this condition in the auricle which is not the site of this impulse formation. Such a functional separation, if complete, as it was in our experiments, should prevent the propagation of impulses from the focus in one auricle to the other. Such was not the case. Flutter

and fibrillation continued at about the same rate in both auricles after such functional separation and the *f*-waves derived by direct leads from both auricles simultaneously were only slightly changed in rate.

It is a remote possibility that the mother ring or single focus was sufficiently extensive so that the crush halved it with consequent small effect. It is difficult to conceive that the ring or focus should always be in the same place, namely, where the auricles were crushed. This is especially unlikely as the crushing forceps were not always applied exactly in the same place or plane. Nor would this explain the slight change in rate of the *f*-waves after crushing. Destruction or modification of the ring or focus should result in a greatly altered electrogram. We have already given our reasons for believing that the trauma from crushing did not, in itself, induce flutter or fibrillation in one or both auricles.

#### CONCLUSION

The conclusion is forced upon us that more than one center or ring must be responsible for auricular flutter or fibrillation. Whether such centers are multiple from the beginning or whether they result from breaking up of an initial impulse into several daughter impulses which shuttle and weave about in both auricles cannot be determined from these experiments. Our experiments do, however, exclude the possibility that only one focus or a single mother ring is responsible for the maintenance of these conditions in the intact heart.

The experiments with ventricular fibrillation are even more convincing because the ventricles were completely separated from one another by cutting. In some instances the entire heart, including the auricles, was cut across along the interventricular septum thus excluding any possibility that impulses were being conducted from one separated ventricle to the other by way of cardiac tissue. The electrograms from each ventricle after such separation were practically the same as before in every experiment. The two halves of the heart could be seen on gross inspection to fibrillate after cutting. The only change to develop was a gradual slowing in each side but this occurred at about the same rate as when the heart was not cut. These experiments are incompatible with the view that ventricular fibrillation in the intact heart is due to a single focus or ring acting as a source for the fibrillary movement.

While our experiments clearly show that a single focus or mother ring cannot possibly be the cause of flutter or fibrillation of the heart and that our results are compatible with the idea that several foci are at work, it must not be construed that our work proves the correctness of the latter view. On the contrary, we feel that much work remains to be done in order to explain the actual fundamental mechanism responsible for this condition.



## RÉSUMÉ

1. The various theories which have been offered to explain flutter and fibrillation of the heart and the arguments *pro* and *con* for each are presented.

2. A series of experiments were designed to test the validity of the various theories. Flutter and fibrillation was induced in the auricles in one series and ventricular fibrillation in another. Control electrograms with direct leads, using nonpolarizable boot electrodes, were recorded from both auricles or from both ventricles. In most cases the records were taken simultaneously. Complete functional or actual separation of one auricle or ventricle from the other was then performed and the electrograms from each were again recorded. The curves show definitely that flutter or fibrillation still continues in each separated chamber. Comparison of the electrograms before and after such separation shows very little change in the rate of the *f*-waves.

3. Such results are obviously incompatible with any theory that flutter or fibrillation in the heart is due to a single focus or a single circus ring sending centrifugal waves into the other auricle.

4. Our experiments are not incompatible with the theory that the impulse becomes broken up into several daughter rings or waves which shuttle and weave about the myocardium. Nor are our results incompatible with the conception that multiple foci may be responsible. It is emphasized, however, that we offer no proof of the correctness of either of these views. On the contrary, we feel that further work is necessary in this direction.

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## CONGENITAL HEART DISEASE

### A CLINICAL AND PATHOLOGICAL STUDY OF TWO CASES OF TRUNCUS SOLITARIUS AORTICUS (PULMONARY ATRESIA)\*

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CONGENITALLY anomalous hearts with a single arterial trunk are not common. These anomalies can be divided into the following groups: (1) true persistent truncus arteriosus; (2) truncus solitarius pulmonalis; (3) truncus solitarius aorticus.

The first group, *persistent truncus arteriosus*, is the least frequent of the three. Feller,<sup>1</sup> in a critical review of the cases reported as truncus communis, could find only a few authentic instances. This abnormality is due to the persistence of the primitive arterial trunk which remains undivided. Here one should expect four cusps to be present. Cases with a persistence of four well-formed semilunar cusps are extremely rare (Abbott,<sup>2</sup> Feller<sup>1</sup>). By means of localization of the ostiae of the coronary arteries and the finding of evidences of fusion of two cusps, Feller was able to determine the previous presence of the four valve cusps in those cases of true persistent truncus in his series where apparently only three were present. The presence of four well-formed cusps associated with a single arterial trunk is usually positive proof of an undivided primitive arterial trunk (Abbott<sup>2</sup>). Nevertheless one occasionally observes instances of a persistent truncus arteriosus with only three semilunar cusps (Abbott<sup>3</sup>).

More frequently, however, one finds that many of the cases wrongly reported as true persistent truncus arteriosus, are in reality cases in which there has been a complete division between the aorta and pulmonary artery, a truncus solitarius aorticus or pulmonalis existing. Due to some congenital malposition of the aortic septum one of the vessels is narrowed and fails to grow normally. This vessel, if obliterated at its orifice, may undergo a complete atresia so that one usually finds a small remnant of the original vessel or even an atresic cord (Abbott<sup>2</sup>). The remaining vessel, aorta or pulmonary artery, dilates.

Atresia of the aorta is much less frequent than that of the pulmonary artery (Abbott,<sup>2</sup> Shapiro<sup>4</sup>). In the cases of atresia of the aorta (*truncus solitarius pulmonalis*) the pulmonary artery enlarges and the sinuses of Valsalva of the enlarged pulmonary artery are free of coronary arteries. The coronary arteries arise from the aortic arch or vestige of the aorta. A complete description and review of the litera-

\*From the Laboratories of the Mount Sinai Hospital, New York City. Aided by a grant from the Lucius N. Littauer Foundation.

ture of this anomaly can be found in the classical monograph of Abbott and also in a recent paper by Shapiro.

The third group, *truncus solitarius aorticus*, which is due to an atresia of the pulmonary artery, is the most frequent of the three. The aorta dilates while the pulmonary artery undergoes progressive atresia. The pulmonary circulation is usually maintained through a widely patent ductus arteriosus, or in some instances, via branches directly from the aorta. This anomaly has been reported by many observers (Mönekberg,<sup>5</sup> Dickson and Fraser,<sup>6</sup> Wheeler and Abbott,<sup>7, 8, 9</sup> and others). Abbott collected 31 cases of this congenital abnormality. Two more cases of atresia of the pulmonary artery recently observed at the Mount Sinai Hospital are added to this group because of the unusual associated anomalies present.

#### CASE REPORTS

CASE I.—Congenital atresia of the orifice of the pulmonary artery, with closed interventricular septum, absence of tricuspid valve, aplasia and aneurysmal dilatation of the the right ventricle, patent foramen ovale and patent ductus arteriosus; truncus aorticus solitarius; single coronary artery; neuroblastoma of adrenal gland with metastases to the liver.

#### CLINICAL HISTORY

R. G., aged six months. Admitted January 19, 1931. Died January 22, 1931.

*Chief Complaint:* Infection of vulva of one week's duration.

*Family History:* Father and mother well.

*Past History:* Full term baby, weighed seven pounds, three ounces at birth. The child had never been ill except for the fact that the cyanosis and dyspnea which were noted at birth had become definitely increased in the last two months.

*Physical Examination:* Well-developed female child who appeared markedly cyanosed. The breathing was rapid. The head appeared small, measuring 40 cm. The chest was round and rather prominent. Both sides were symmetrical. There was definite cyanosis and clubbing of both fingers and toes. The heart was enlarged to percussion both to right and left. There was a marked rough systolic murmur heard best over the second interspace on the left side transmitted toward the apex. The rate was rapid and the rhythm regular. Dr. S. Karelitz noted that the systolic murmur had a peculiar resonant quality, almost like that heard in an aneurysm. It was his impression at that time that there was a congenital heart disease with pulmonic stenosis, tremendous enlargement, especially of the right heart, and most likely other cardiac anomalies. The liver was palpable one and a half fingerbreadths below the costal margin. The child remained in the hospital for three days and succumbed to an erysipelas of the vulva.

#### Blood count:—

|                    |             |
|--------------------|-------------|
| R.B.C.             | 5,300,000   |
| W.B.C.             | 15,000      |
| Polymorphonuclears | 52 per cent |
| Monocytes          | 3 per cent  |
| Lymphocytes        | 45 per cent |

*Roentgen Examination:* January 20, 1931 (M. L. Sussman, M.D.): Examination of the chest showed no abnormality in the lungs. The heart was markedly en-

larged. The enlargement was general but particularly upward and to the right, in which region it assumed a globular appearance, the upper margin of the cardiac shadow reaching well up to the second rib posteriorly. The cardiophrenic angle on this side was perfectly clear. On the left side the cardiac contour appeared to consist of two curves, the point of union being suggestive of the junction of two chambers. (Fig. 1.)

The findings were extremely atypical, the enlargement upward and to the right being of the appearance often seen with extreme enlargement of the left auricle. The general configuration, however, was very strongly suggestive of a congenital heart lesion. Heart measurements were: Ml 4.3; Mr 5.7; T 10.0; Chest 14 cm. Film taken at 40 inches.



Fig. 1.—Roentgen ray appearance of chest. (Case I.)

*Autopsy* (Performed by Dr. P. Klemperer).—The body was that of a six months' infant, well developed, well nourished and in incomplete rigor mortis. There was a mottled purplish area of discoloration about the size of a twenty-five cent piece on the right side of the vulva.

*Lungs:* Grossly normal.

*Heart:* The heart\* presented externally a very unusual appearance. The region usually occupied by the right ventricle was totally collapsed and gave the appearance of a cyst which was separated from a smaller multilocular cyst. The latter formed the apex of the right ventricle and had several communications with the main cavity of the right ventricle (Fig. 2).

The heart measured 4.5 cm. in diameter at its base. The pericardium was smooth and glistening. At the base of the heart there was only one large vessel

\*The specimens were paraffinized by the method described by Gross and Leslie.<sup>12</sup> This facilitated the study of the specimens.

which seemed to arise from the left ventricle. The right auricle was unusually large. Its cavity was about the size of the dilated right ventricle. The wall of the right auricle was hypertrophied, measuring 0.2 cm. The musculi pectinati were well developed. The superior and inferior venae cavae entered the right auricle in their usual position. Instead of the tricuspid leaflets one found only a sharp ridge at the site of the auriculo-ventricular sulcus in its internal aspect. The tricuspid valve, chordae tendineae, and papillary muscles were completely lacking. The cyst seen externally was in reality a dilated right ventricle whose wall was extremely thin, measuring roughly 0.05 cm.

In attempting to trace the circulation from the right ventricle upward, it was found that there was no opening from the ventricle either into a pulmonary artery or aorta and that there was no defect anywhere along the interventricular septum (Fig. 3). The foramen ovale, however, was widely patent.

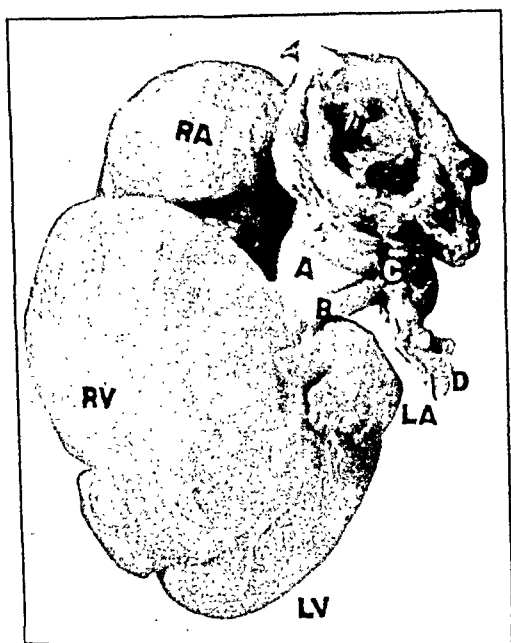


Fig. 2-A.

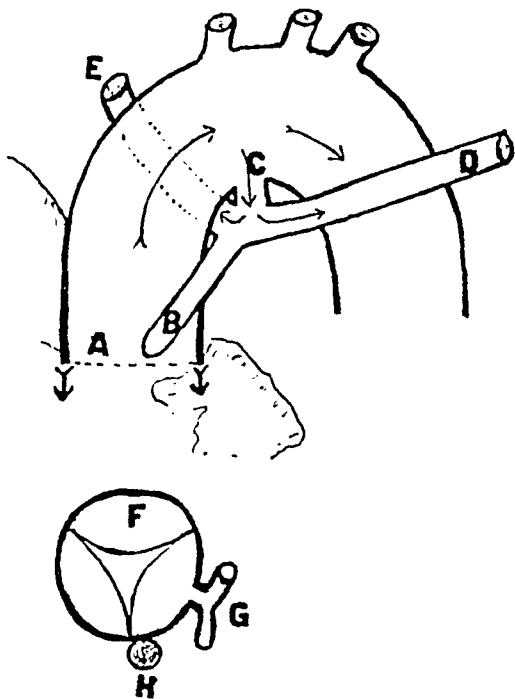


Fig. 2-B.

Fig. 2, A and B. Photograph of parafronized heart, with diagram showing relationship of aorta to pulmonary artery. Key to Fig. 2, A and B: A, aorta; B, atresic pulmonary artery; C, patent ductus arteriosus; D, left pulmonary artery; E, right pulmonary artery; F, cross section of aorta near origin; G, single coronary artery; H, cross section of atresic pulmonary artery near origin; R.A., right auricle; L.A., left auricle; L.V., left ventricle; R.V., right ventricle.

The left auricle was very small in size, the transverse diameter of its cavity being less than one centimeter as compared to 3.25 cm. of the right. The left auricle received pulmonary veins from both lungs. The mitral ring was small but the mitral cusps, chordae tendineae, and papillary muscles were well developed. The wall of the left ventricle, as well as that of the interventricular septum measured 0.4 cm. in thickness. Arising in its usual position from the left ventricle there was one large vessel (aorta) with three cusps: one right anterior, one left anterior, and one posterior. A coronary artery arose in the sinus of the cusp situated to the left (Fig. 2-B). This coronary vessel seemed to be the only artery supplying the heart. At the under surface of the arch the aorta gave off one vessel (patent ductus arteriosus) which branched three ways, one branch going to the left lung,

another branch going posteriorly to the right lung, and a third branch coursing downward and terminating anteriorly to the right of the aorta at its base. On cross section this vessel was the pulmonary artery which had undergone atresia with a complete obliteration at its base. Arising in the usual fashion from the arch of the aorta were the innominate, left common carotid, and subclavian arteries.

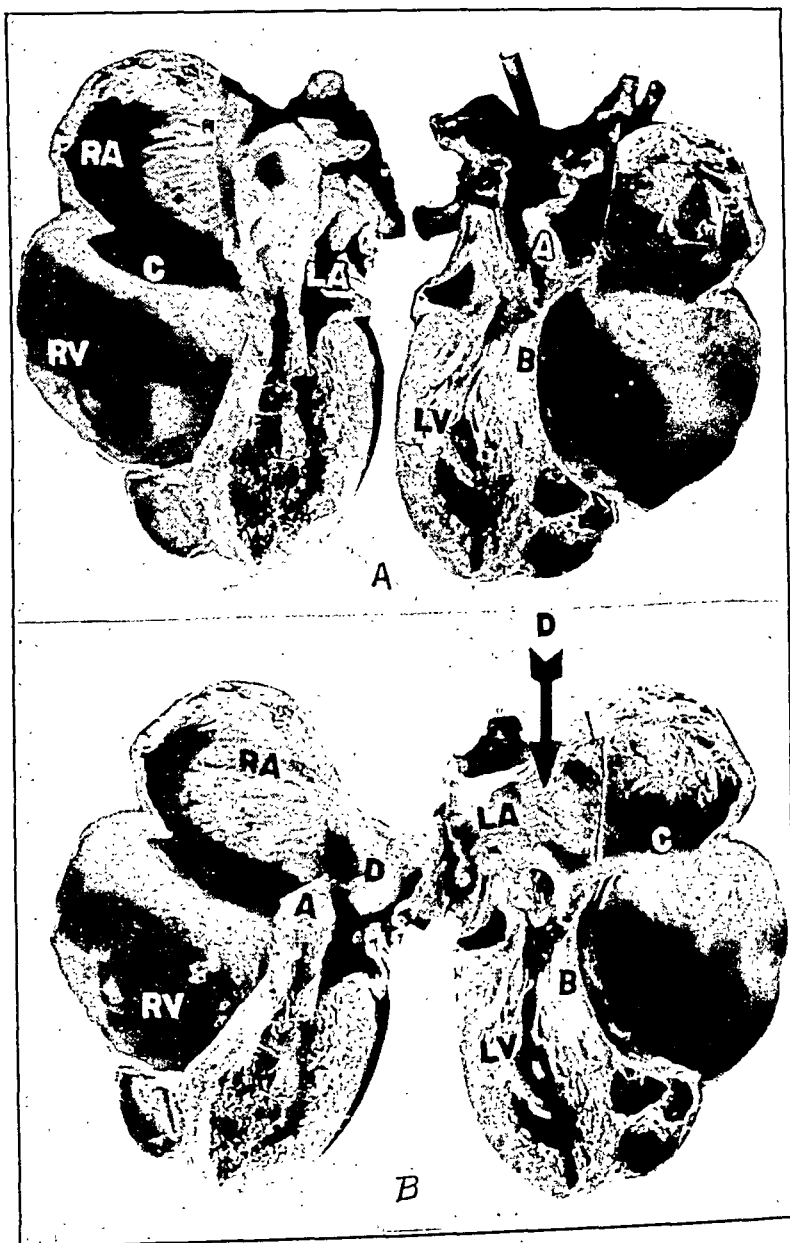


Fig. 3-A.—Photograph of sagittal section of anterior portion of heart, showing single arterial trunk, the auricular and ventricular cavities, as well as closed interventricular septum.

Fig. 3-B.—Photograph of sagittal section of the posterior portion of heart with widely patent foramen ovale. Key to Fig. 3. A and B: A, aorta; B, closed interventricular septum; C, tricuspid valve; D, widely patent foramen ovale; R.A., right auricle; L.A., left auricle; L.V., left ventricle; R.V., right ventricle.

The course of circulation in this heart was, therefore, from the right auricle through the auricular septal defect into the left auricle downward into the left ventricle. From there on, the mixed blood of the right and the left hearts passed into the aorta, part going into the systemic circulation, part passing through the

patent ductus arteriosus into both pulmonary arteries supplying the lungs. The right auricle and left ventricle apparently carried on the main burden of the circulation. The right ventricle was a blind pocket.

#### MICROSCOPICAL SECTIONS

*Heart.*—Left Ventricle and Right Auricle.—The muscle fibers were well formed, and the nuclei were prominent. There was no evidence of scarring or inflammation. The coronary arteries and branches were normal.

*Auriculo-ventricular Sulcus (Right).*—A section taken through the ridge where the tricuspid valves normally arise showed a thickened fibrous layer arising at the point where the right auricle meets the right ventricle. The fibrous layer projects for a short distance where it was covered by the endocardium. There were no evidences of inflammation. In the pericardium of the auriculo-ventricular sulcus a large coronary artery was seen.

*Right Ventricle.*—The musculature of the right ventricle was compressed between a thickened and elasticized endocardium and the thickened fibrous visceral pericardium. The greater portion of the wall of the right ventricle was fibrous and elasticized, with little or no musculature present.

*Adrenal Gland.*—Examination of the left adrenal gland revealed that it was enlarged to the size of a walnut and measured 3.5 by 3.0 by 3.5 cm. The medial border of the tumor-like enlargement of the gland presented a thin margin of normal appearing adrenal tissue. Section of the gland revealed a walnut-sized tumor mass occupying the entire medullary space. It presented a mottled grayish-pink and dark red color, rather firm in consistency with a few yellow areas (possibly necrotic tissue). The medial edge, as has been stated, was composed of normal appearing adrenal tissue, especially cortex. The cortical tissue entirely surrounded the tumor but in the distal portions was very much thinned out, appearing like a ball surrounded by a cover with a dense accumulation of the covering at one end. The right adrenal gland presented no abnormal findings. Weight, 20 grams.

*Liver.*—The liver was somewhat enlarged, especially the right lobe. On the surface of the liver a few small pearly grayish-pink depressed areas, varying in size from 2 to 8 mm. could be seen. Cross section revealed a number of these nodules scattered in the liver parenchyma, a few being superficial. The right lobe presented a diffusely fatty appearance, parboiled, and glassy. The left lobe of the liver also showed a few metastatic nodules but the liver parenchyma was dark red and the normal architecture was very indistinct because of the marked congestion. The hepatic artery, portal vein, and hepatic veins were negative. The gall bladder and bile ducts presented no abnormal findings.

*Kidneys.*—The left kidney showed normal fetal markings. Cut section revealed only congested parenchyma. The renal artery and vein showed no abnormalities. The superior surface of the kidney had been flattened by the left adrenal tumor mass. The right kidney was found at the brim of the pelvis anterior to the aorta. A single right renal artery could not be found. Main branches from both the right and left common iliac artery were seen entering the kidney, that from the right entered the anterior surface of the kidney after coursing down the posterior surface and entering the hilus which was on the lateral border of the kidney. The branch from the left common iliac artery entered directly into the renal substance on its posterior surface in its midportion. The right ureter entered the kidney on the lateral surface somewhat anteriorly and in front of the branch of the right common iliac artery. Except for its anomalous arterial circulation, the kidney appeared normal both on its surface and on cross section. The right renal vein came from the hilus to enter the inferior vena cava at a somewhat lower level.

*Diagnosis.*—(1) Congenital malformation of the heart; (2) atresia of the pulmonary artery at its mouth without interventricular septal defect; (3) aplasia and marked dilatation of the right ventricle; (4) patent foramen ovale; (5) absence of tricuspid valve and its chordae tendineae and papillary muscles; (6) truncus solitarius aorticus; (7) patent ductus arteriosus; (8) single coronary artery.

Neuroblastoma (left adrenal gland) with metastases to liver; chronic passive congestion of liver, spleen, and kidneys; degeneration of liver, and erysipelas of right vulva (clinically).

**CASE II.** Congenital atresia of the orifice of the pulmonary artery, truncus aorticus solitarius (patent ductus arteriosus), interventricular septal defect. Single coronary artery.

#### CLINICAL HISTORY

L. S., aged three months. First Admission: February 28, 1930. Dismissed: June 9, 1930.

*Chief Complaint:* Cough and fever.

*Family History:* Entirely negative.

*Past History:* Child of three months, with a history of cyanosis since birth. Both history and development of the child were normal.

*Physical Examination:* The outstanding feature was cyanosis of the lips and extremities, which was marked when the child cried or strained. There was distinct clubbing of the fingers. There was no dyspnea or edema. The liver was felt one finger below the costal margin. Examination of the chest showed dullness in the R. U. L. with some higher pitched breathing but no râles. The cyanosis was thought to be due to a congenital cardiac lesion and an atelectasis of the lungs. The heart did not appear enlarged on percussion. It was regular and no murmurs were heard.

#### Blood:

|                    |             |
|--------------------|-------------|
| Hgb                | 88 per cent |
| R.B.C.             | 5,600,000   |
| W.B.C.             | 8,700       |
| Polymorphonuclears | 46 per cent |
| Lymphocytes        | 44 per cent |
| Monocytes          | 6 per cent  |
| Eosinophiles       | 2 per cent  |
| Basophiles         | 2 per cent  |

Wassermanns of mother, father, and child were negative.

*Second Admission:* January 26, 1931. Died: January 27, 1931.

The child was perfectly well until three days before its second admission (at the age of ten months) when it developed cough, fever, dyspnea, and increased cyanosis, and succumbed the following day to a bronchopneumonia.

X-ray examination and fluoroscopy, as well as physical examination confirmed the impression that one was dealing with a congenital heart condition.

*Autopsy* (Performed by Dr. P. Klemperer).—Body was that of a well-developed infant with marked cyanosis and clubbing of finger tips.

*Abdomen:* Situs viscerum normal. No ascites present.

*Thorax:* There was a moderate beading of ribs. A section of a costochondral junction showed irregular line of bone formation extending into the cartilage with a widened zone of ossification. The pleural cavities were free. The lungs externally showed congestion of R. U. L. and R. L. L., with increased firmness of texture.

*Heart:* The heart was globular and its apex was made up of the left ventricle. The pericardium was smooth and glistening. Externally, there seemed to be only



one large vessel at the base of the heart. The width of the heart at the base was 4 cm.; from the base to the apex the heart measured 4.5 cm. (Fig. 4.)

On sagittal section the heart had four chambers. The right auricle received the superior and inferior venae cavae in the usual sites. The right auricle and tricuspid valve presented no abnormalities. The right ventricular cavity was smaller than the left. The wall thickness measured 0.4 cm. There was a defect 0.5 cm. in diameter in the intraventricular septum at its anterior superior aspect just below the origin of the aorta (Fig. 5-A and B). The left auricle was smaller than the right and received pulmonary veins from both lungs. The interauricular septum was completely closed. The mitral valve, chordae tendineae, and papillary muscles were well developed. The musculature of the left ventricle was compact. The wall measured 0.4 cm.

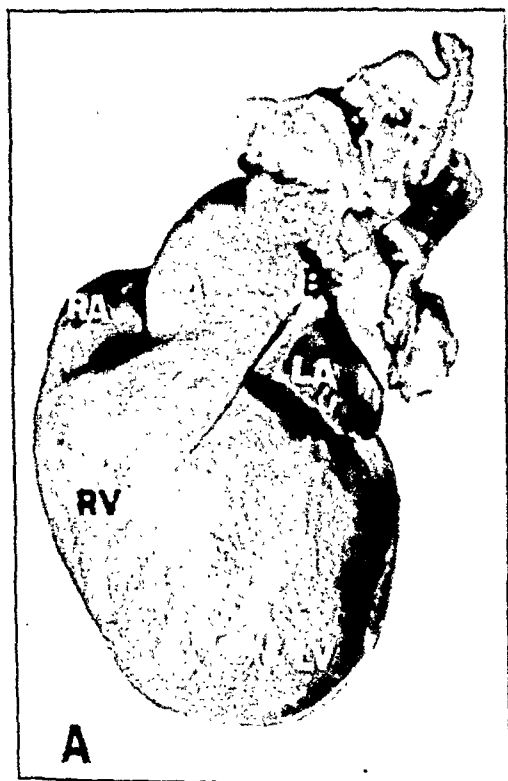


FIG. 4-A.

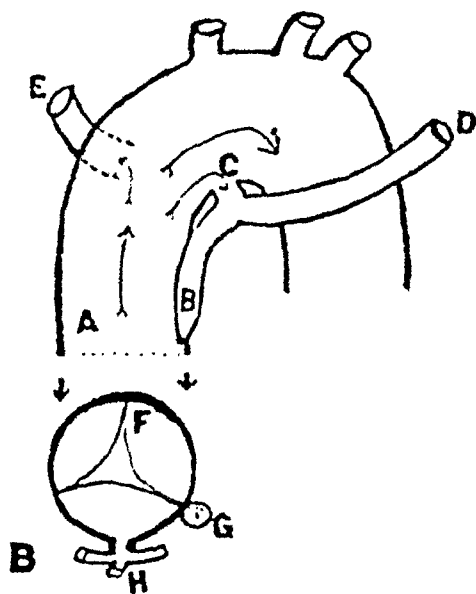


FIG. 4-B.

Fig. 4, A and B.—Photograph of parafronzed heart (anterior view) with diagram showing the relationship between aorta and pulmonary artery. Key to Fig. 4, A and B: A, aorta; B, atresic pulmonary artery; C, patent ductus arteriosus; D, left pulmonary artery; E, right pulmonary artery; F, cross section of aorta near origin; G, cross section of atresic pulmonary artery near origin; H, single coronary artery; R.A., right auricle; L.A., left auricle; L.V., left ventricle; R.V., right ventricle.

Riding above and to the right of the interventricular septal defect was the large aortic trunk which had three cusps, one anterior and two posterior of equal size (Fig. 4-B). From the sinus of Valsalva of the anterior cusp was a large opening for the coronary artery. This was the only coronary artery that could be found arising from any of the vessels in or near the heart. This coronary vessel, therefore, seemed to be the sole arterial supply to the heart. On the under surface of the aorta near the arch there arose one small branch which went directly to the right lung. On the left side there was another branch (patent ductus arteriosus) which, shortly after leaving the aorta, gave rise to one vessel going upward and backward to the left lung and another vessel which coursed downward and terminated

to the left of the aorta about 1 cm. from its base. On cross section, this latter vessel (atresic pulmonary artery) was seen to end in a blind pocket, with a few puckerings at its base suggestive of regressed or incompletely formed valves.

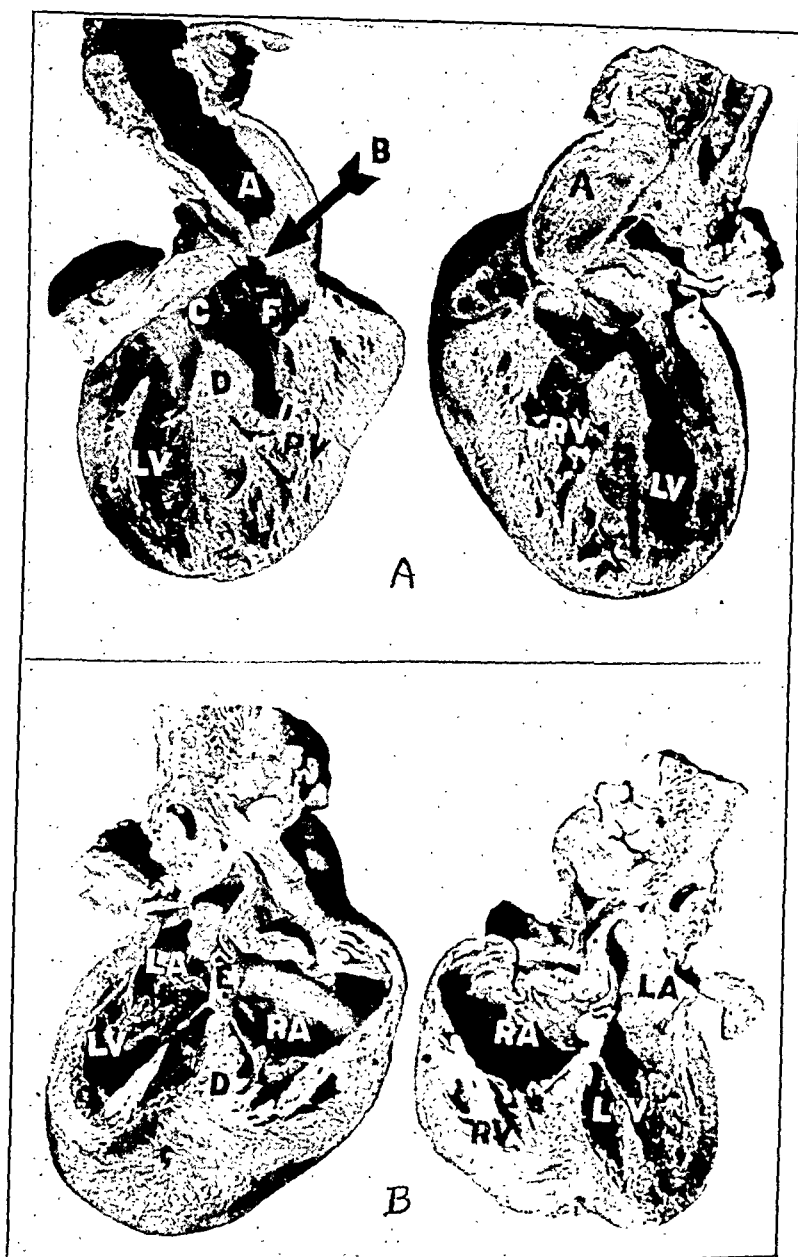


Fig. 5-A.—Photograph of sagittal section of anterior portion of heart showing single arterial trunk overriding an interventricular septal defect. Note single coronary orifice.

Fig. 5-B.—Photograph of sagittal section of posterior portion of heart, showing closed interauricular septum. Key to Fig. 5, A and B: A, aorta; B, orifice of single coronary artery; C, interventricular septal defect; D, interventricular septum; E, interauricular septum; F, aortic valve cusps; L.A., left auricle; R.A., right auricle; L.V., left ventricle; R.V., right ventricle.

The truncus showed evidence of incomplete rotation, in that the right coronary artery came off anteriorly\* and the termination of the atresic portion of the pulmonary artery was situated more to the left.

\*Considered anatomically with reference to the heart and not with reference to the body.

The innominate arteries, the left common carotid artery, and the left subclavian artery arose from the arch of the aorta, in their usual position.

*Heart.*—(Microscopical sections.) Sections through myocardium showed no evidences of inflammation, or other pathological changes.

*Inferior Vena Cava.*—Negative.

*Liver.*—Somewhat enlarged. The lower margin was thin. The surface was normal. Section revealed marked loss of lobular markings, yellowish color and parboiled appearance of parenchyma. The portal vein, hepatic artery, gall bladder, and bile ducts were all normal.

*Spleen.*—Distinctly enlarged, firm, dark. The cut surface showed congestion with distinct enlargement of follicles, and did not scrape. A small accessory spleen was seen in the hilus. The splenic vein was normal.

*Kidneys.*—Fetal lobulations were distinct. The cut section revealed moderate congestion. The right renal artery was double immediately after its origin in the aorta. The left was normal. Ureters and bladder were normal. The urethra was long but free of anomaly.

*Adrenal Glands.*—Normal in size.

*Thymus.*—Not excessively enlarged.

*Gastrointestinal Tract.*—The esophagus and stomach were normal. The small intestine showed marked hyperplasia of lymphoid tissue throughout, including Peyer's patches and solitary follicles. The large intestine was essentially similar.

*Diagnosis.*—(1) Congenital malformation of the heart; (2) atresia of the pulmonary artery; (3) truncus aorticus solitarius; (4) patent ductus arteriosus; (5) subaortic interventricular septal defect; (6) single coronary artery.

Bronchopneumonia R. U. L. and R. L. L.; acute bronchitis; chronic passive congestion of liver, spleen, kidneys, gastrointestinal tract, and pancreas; degeneration of liver; follicular hyperplasia of small and large intestines and spleen; mild rickets; and accessory spleen.

#### SUMMARY

Atresia of the pulmonary artery is a relatively uncommon condition. In the cases with a defect in the interventricular septum, the average duration of life is three and four-tenths years according to the statistics collected by Abbott<sup>2</sup> in a review of 24 cases. The maximum age reached was thirteen years. In our Case 2 the child lived up to ten months. Its death was hastened by a mild bronchitis and bronchopneumonia.

This anomaly is far more serious when associated with a closed interventricular septum. Of the 7 cases collected by Abbott, the average duration of life was twelve weeks, with a maximum age period of six months. Our Case 1 lived six months with symptoms of progressive heart failure and increasing cyanosis and dyspnea, finally succumbing to an erysipelas.

Clinically, both children were cyanotic at birth. When admitted to the hospital, cyanosis, distinct clubbing of the fingers, and enlargement of the liver were noted. These symptoms were, however, more intense in Case 1, with the intact interventricular septum. Here, also, the diagnosis of a congenital cardiac defect was aided by the extreme enlargement of the organ and by the presence of a rough systolic

murmur with a peculiar resonant quality suggestive of an aneurysm, heard best over the second interspace on the left side and transmitted to the apex. The x-ray film of the heart presented an unusual appearance, that of a large egg occupying almost the entire chest wall (Fig. 1). The correlation of the x-ray findings with the post-mortem findings showed the enlargement to be due to the aneurysm of the right ventricle and the dilated and hypertrophied right auricle. It was also possible to distinguish both ventricles on the x-ray plate.

In the case with the defect in the interventricular septum no enlargement of the heart was noted, neither were there any murmurs heard. Zimmerman<sup>11</sup> recently reported a case of truncus arteriosus communis with an interventricular septal defect in a colored male of twenty-five years, the cause of whose death was an automobile accident. Considered from the point of view of mechanics of circulation, Zimmerman's case is similar to our second case in which the baby lived to the age of ten months. A case reported by Wheeler and Abbott<sup>7</sup> of pulmonary atresia and other cardiac anomalies survived until the age of twenty-nine.

The absence of one coronary in both cases is an unusual anomaly which is extremely rare in otherwise normal hearts. It is well known that one coronary artery can be an adequate source of blood supply to maintain intracardiac circulation, provided there are sufficient anastomoses.<sup>12</sup> This fact is well demonstrated by Case 2 in which both ventricles were well developed. Microscopical examination of the myocardium showed no evidences of degeneration or scarring.

The case with the closed interventricular septum and marked dilatation of the aplastic right ventricle with aplasia of the tricuspid valves is puzzling. The most obvious explanation as to the cause of the aplasia and dilatation of the right ventricle is a nutritional disturbance and the increased intraventricular pressure necessary to force blood into the left side of the heart.

It is also possible that in this case the pulmonary artery was originally patent though incompletely developed. The right coronary artery may have had an abnormal origin from this vessel. With increasing stenosis of the pulmonary artery two phenomena arose: namely, the right coronary supply became insufficient and the right ventricle had to overcome the pressure of the left heart in order to force blood through the foramen ovale. Possibly both of these factors led to the final aplasia and dilatation of the right ventricle.

While it is impossible to find traces of this hypothetical right coronary artery in this case, it is to be noted that a case of aplasia of the right ventricle occurring with atresia of the pulmonary artery and closed interventricular septum described by Abbott apparently possessed two coronary arteries arising from the aorta and, secondly, cases with abnormal origin of one coronary artery from the pulmonary

artery described by Abrikossoff,<sup>13</sup> Heitzmann,<sup>14</sup> Krumbhaar,<sup>15</sup> Schley<sup>16</sup> and Scholte<sup>17</sup> showed evidences of myocardial degeneration and extensive fibrosis in the areas supplied by the misplaced coronary artery.

In the case described by Abrikossoff, aneurysmal dilatation of the left ventricle was associated with a misplaced coronary artery arising from the pulmonary artery.

The association of cardiac anomalies with abnormalities elsewhere in the body has been frequently emphasized. Other anomalies were present in both of our cases. Of special interest, however, was the presence of a neuroblastoma of the adrenal gland with metastases to the liver in Case 1, a child of *six months*.

The author is indebted to Dr. Louis Gross and Dr. Maude E. Abbott for their advice and criticism, to Dr. Bela Schick for the use of clinical material, and to Dr. Leopold Jaches for the use of the x-ray material.

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# Department of Clinical Reports

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## PROLONGED PAROXYSMAL TACHYCARDIA

### CASE REPORT\*

B. E. HAMILTON, M.D., AND D. HURWITZ, M.D.

BOSTON, MASS.

### CASE REPORT

**M** B., cobbler, aged fifty years, an Armenian, entered the Second Medical Service of the Boston City Hospital on September 22, 1930. The history was obtained with difficulty because the patient spoke very little English. He had been in good health and had worked continuously until two weeks before entrance. At this time, following a heavy meal, the patient was seized with cramp-like pains in the umbilical region, later rising to the epigastric region. The pain fluctuated in severity, but persisted.

At entrance, the physical examination was unimportant, except that the pulse rate was 180 per minute. The rhythm was regular. The blood pressure was 95/85 millimeters of mercury. The respirations were 28 per minute. A few crepitant râles were heard at both bases posteriorly. Slight tenderness was elicited in the epigastrium. An electrocardiogram taken September 22 showed paroxysmal tachycardia, probably auricular in origin. The rate was 200 per minute.

Though it was believed that the patient had had a coronary occlusion, no evidence appeared to support this suspicion. There was no fever. The white blood cell count at entrance was 10,500 per cubic millimeter of blood. Later, it fell to 4,000 per cubic millimeter of blood. The paroxysmal tachycardia persisted for thirty-five days. The only change in his condition throughout the thirty-five days was gradually increasing congestive failure until the liver was definitely engorged and slightly tender; the râles at the lung bases increased, and a small amount of demonstrable fluid appeared at both bases. Curiously, there was more on the left than on the right.

During the thirty-five days, he received the following medication: quinidine sulphate, 30 grains each day for two days, was given first, without effect on the heart. This was stopped because of nausea and vomiting. Two doses of digitalis were given intravenously. The first dose was 9 grains. The second dose, given twenty-four hours later, was 10 grains. There was no appreciable effect. The following day powdered digitalis, 9 grains, was given by mouth. This dose was repeated each day for three days. The dose was then reduced to 4½ grains daily. This was continued for eleven days. The dose was then reduced to 1½ grains daily. Throughout this time, the patient was under close observation. His heart rate was counted every hour throughout the twenty-four hours. There was no appreciable effect from the digitalis. The digitalis was discontinued three days

\*From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard) of the Boston City Hospital.

before the paroxysm ceased. Quinidine sulphate, 6 grains in one dose, was given intravenously fourteen days after admission, two days after the dose of digitalis had been reduced to  $4\frac{1}{2}$  grains daily. The cardiac rate dropped from 180 per minute to 150 per minute in five minutes and then returned to 180 per minute gradually in twenty minutes. Forty-eight hours before the paroxysm ceased, quinine hydrochloride was given by mouth in 10-grain doses. An electrocardiogram taken after the first two or three doses showed a rate of 176 per minute, which was slightly lower than the average rate. After he had had a total of 70 grains of quinine hydrochloride over a period of forty-eight hours, his heart suddenly resumed a normal rhythm with a rate of 80 per minute. There was immediate improvement in

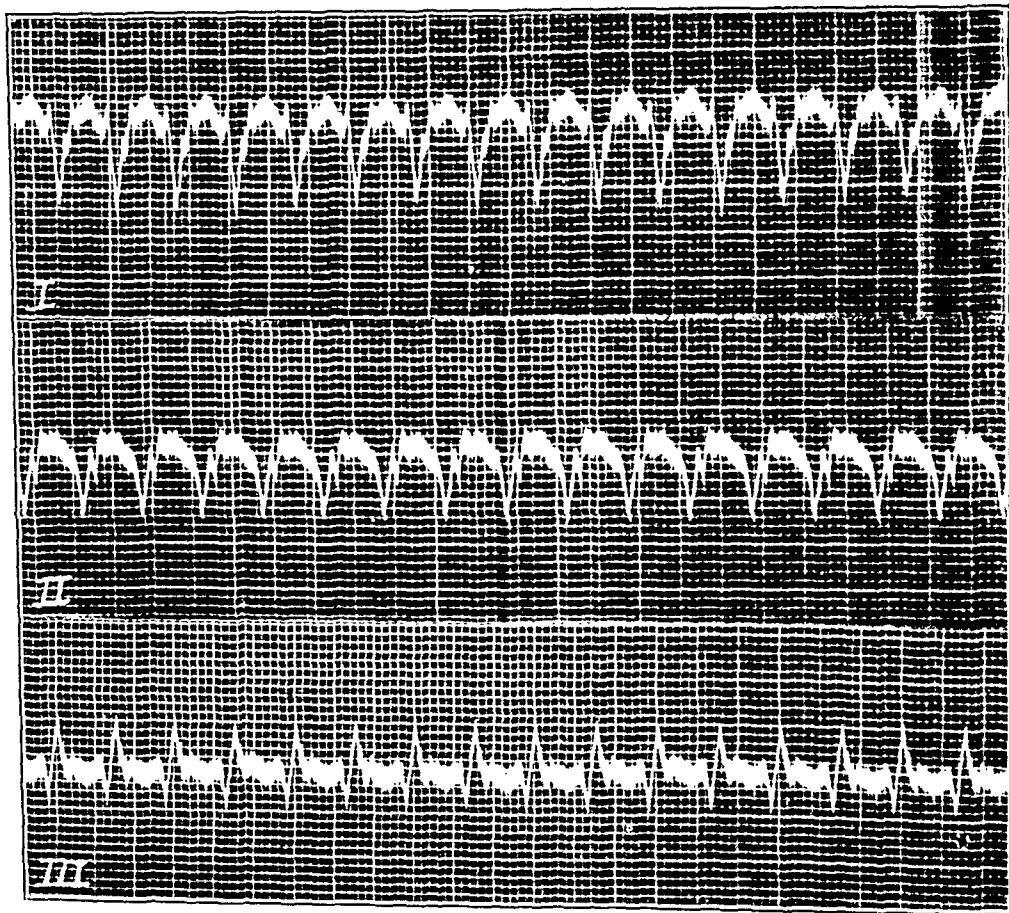


Fig. 1.—Sept. 22, 1930. Paroxysmal tachycardia, probably auricular. Rate 200. ? P-waves Lead III. QRS = 0.12 sec., slurred in all leads. T opposite main deflection in all leads. Right bundle-branch block (if tachycardia is auricular in origin.)

symptoms. During the next few weeks, his congestive failure cleared, and he was discharged in apparently good condition four and a half weeks after his return to normal cardiac rhythm.

On April 4, 1931, five months after discharge, he was readmitted to the hospital acutely ill. Following his first discharge from the hospital, he had been able to return to work and had been without symptoms until a few hours before his readmittance. He entered the hospital in a condition of shock. The temperature, by mouth, was 96 degrees Fahrenheit. The pulse rate was 65 per minute. The respirations were 30 per minute. The white blood count was 20,000 per cubic millimeter of blood. He lived only six hours following admission to the hospital.

*Post-mortem Examination of Heart.*—The weight was 360 gm. The organ was essentially normal in size. The epicardium was smooth but showed slight discoloration over the posterior portion of the left ventricle. The myocardium was pale greyish red in color and was markedly scarred. Immediately below the mitral ring, extending posteriorly as far as the interventricular septum, and inferiorly as far as the apex, there was a pear-shaped area approximately 5 or 6 cm. in diameter where the myocardium was thinned, mottled yellowish grey in color, containing hyalin appearing bands; the thickness at this point was 0.7 cm. The valves were negative with the exception of slight atheroma of the aortic. The aorta immediately above showed marked thickening of the intima, with the formation of plaques and nodules some of which were yellow in color and appeared atheromatous; others were bluish in color and hyalin in appearance, giving the appearance

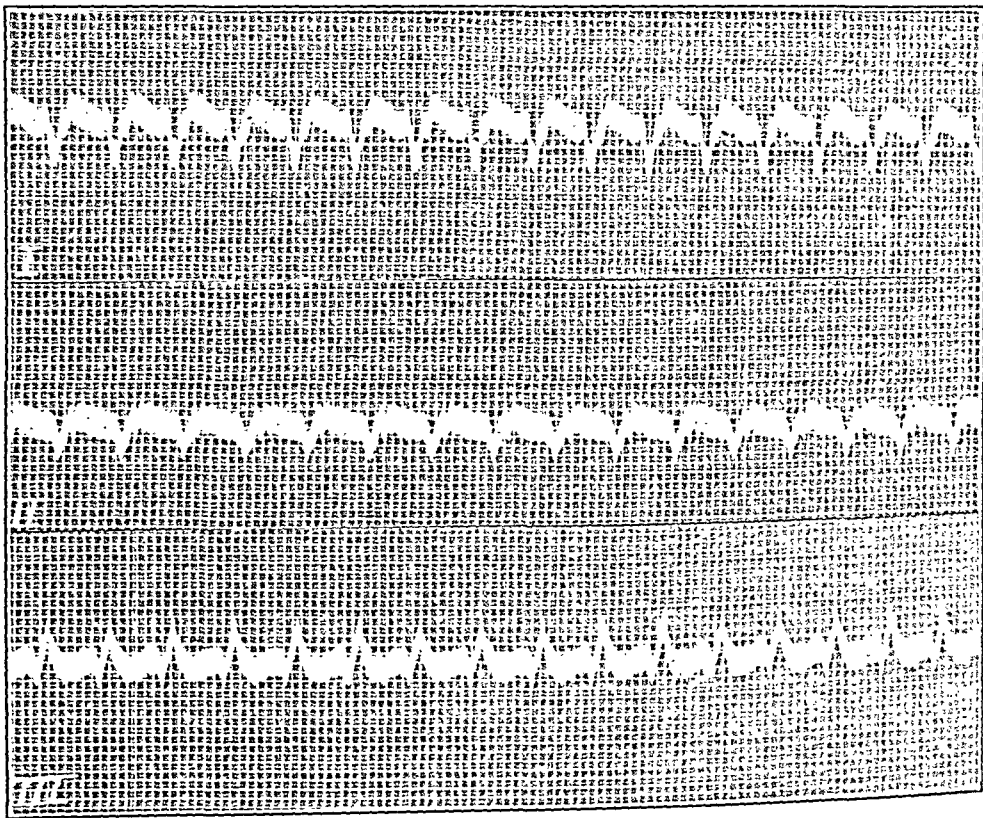


Fig. 2.—Oct. 10, 1930. Paroxysmal tachycardia, probably auricular. Rate 200. ? P-wave Lead III. QRS = 0.12 sec. slurred in all leads. Right bundle-branch block (if tachycardia is auricular in origin). Low amplitude (maximum 5 mm.).

of syphilis. The mouths of both coronaries were patent but thickened. The right coronary at the level of the tricuspid valve showed almost complete occlusion. The vessel at this point was yellowish grey in color and appeared hyalinized. Beyond this point the lumen was patent but very narrow. The interventricular portion of the left coronary about 2.5 cm. from its point of origin showed an occlusion by a red, soft thrombus; beyond, the vessel wall was thickened but patent. The circumflex branch of the left coronary 1 cm. from its point of origin showed complete occlusion, from an old process. The healed infarcted area described above lay below.

During the patient's stay in the hospital, he was under the care of Drs. L. B. Ellis, B. E. Hamilton, D. Hurwitz, W. R. Ohler, W. H. Robey, and F. W. White. The electrocardiograms were taken and interpreted under the direction of Dr. J. M. Faulkner. The post-mortem examination was made by Dr. J. M. Woodall.



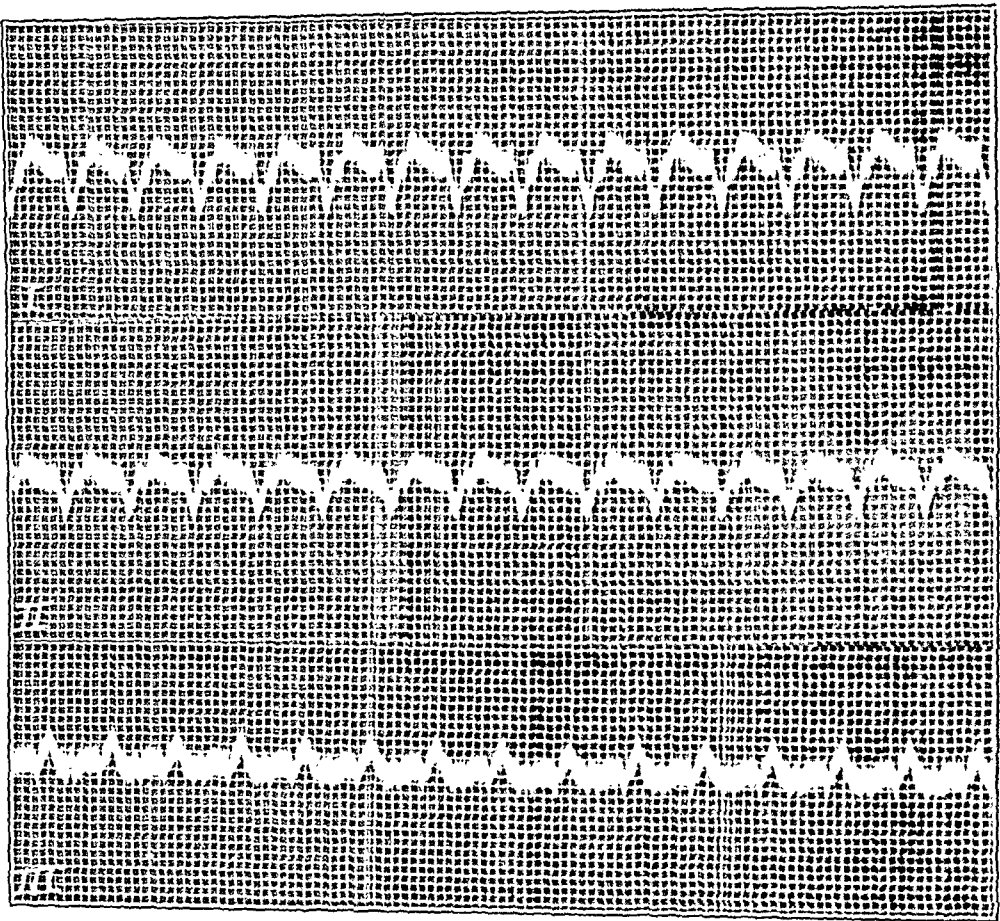


Fig. 3.—Oct. 18, 1930. Paroxysmal tachycardia, probably auricular. Rate 200 ? P-waves Lead III. QRS = 0.12 sec., slurred in all leads. T opposite main deflection in all leads. Right bundle-branch block (if tachycardia is auricular in origin). Low amplitude (maximum 4.5 mm.).

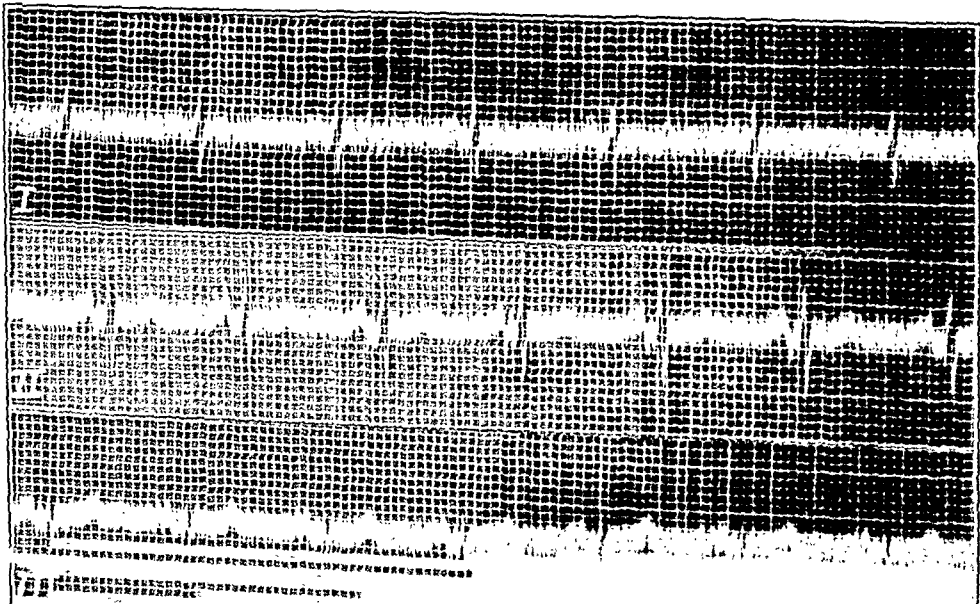


Fig. 4.—Nov. 20, 1930. Normal sinus rhythm. Rate 94. PR = 0.12–0.15 sec. T<sub>1</sub> inverted, T<sub>2</sub> T<sub>3</sub> upright. Axis normal. Low amplitude (m.).

## COMMENT

The important findings are:

1. *Duration of paroxysmal tachycardia.*—Though it is known that paroxysmal tachycardia may continue indefinitely, a duration of more than a few days is rare and very few cases have been reported with a known duration of thirty-five days with recovery. The attack may have been present during the two weeks before admission, making a possible total of forty-nine days.

2. The patient was not conscious of his tachycardia. He complained only of gastrointestinal disturbance.

3. The paroxysmal tachycardia was probably associated with a coronary occlusion with infarction. This was indicated by the subsequent post-mortem examination. There was no clinical evidence to confirm this diagnosis, except the unexplained paroxysmal tachycardia itself. The gastrointestinal discomfort might have been the result of the paroxysmal tachycardia alone. So far as is known, this is the first and only attack of paroxysmal tachycardia that the patient had.

4. Digitalis and quinidine sulphate by mouth and digalen intravenously were not followed by any appreciable change in rate. Quinidine sulphate intravenously caused a reduction in rate for twenty minutes only. Quinine hydrochloride by mouth was accompanied by some slowing of rate and a return to normal rhythm.

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## Original Communications

### SOME CARDINAL CIRCULATORY SYNDROMES\*

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PRIOR to the final decade of the past century, slowing of blood flow was almost invariably attributed to cardiac weakness. Since then, studies on circulatory collapse in infectious diseases and traumatic shock have led to general recognition of the manifestations of circulatory failure initiated in the periphery. There have also been attempts, especially in France, to differentiate the clinical pictures characterizing failure of the individual ventricles and auricles of the heart. These teachings have not been widely adopted in this country, and many regard the distinctions as artificial.

In the following pages, the attempt will be made to demonstrate the feasibility and the utility of differentiating individual types of cardiac failure, each with a characteristic clinical picture resulting from a well-defined aberration in the dynamics of the circulation. Together with the failures of peripheral genesis, these constitute what we may term the *cardinal circulatory syndromes*. Preliminary to discussion of these cardinal circulatory syndromes, it may be well to describe briefly some of the means by which the heart accommodates itself to increased work.

To a large extent, the changes in the dynamics of the circulation in disease are merely exaggerations of the accommodative reactions in health.

#### DILATATION OF THE HEART

Older clinicians viewed dilatation of the heart as a passive process resulting from defective contractility or tons of the myocardium. For several decades, however, the view has steadily gained ground that cardiac dilatation is a useful adaptation playing a fundamental part in the adjustment of the heart to increased work. Originally reached on purely clinical grounds, this conception has acquired a sound foundation through experimental investigations of physiologists on the dynamics of the heart.

\*Read at the Graduate Fortnight of the New York Academy of Medicine, October 27, 1931.

These studies have shown that when either heightened arterial resistance or greater venous inflow increases the work of the heart, accommodation to the greater load involves increase in diastolic volume. Starling<sup>1</sup> found that when arterial resistance is increased, the heart fails to empty as completely during the first beats, so that the residual blood in the chamber at the end of systole is increased. Inasmuch as the venous inflow during diastole remains constant, the result is increased diastolic volume. However, as the diastolic volume mounts with successive beats, the output also rises until equilibrium is attained by output equalling inflow. There is a similar process of adaptation when the arterial resistance is constant but the venous inflow rises. In both cases, the adaptation to greater work accompanies larger diastolic volume of the heart, i.e., increase in the initial length of the muscle fibers. The mechanism by which this greater initial length of the muscle fiber causes it to contract more forcefully is in dispute. According to Starling,<sup>1</sup> it is the greater *length* of the fiber as such that causes it to free more energy when shortening, while Frank<sup>2</sup> and others believe that the heightened initial *tension* of the fiber is the coefficient that results in the more powerful systole.

Whichever of these views is correct, it is significant for the clinician that the adaptation of the heart to increased work involves at least diastolic dilatation. The compensatory significance of the dilatation of the appropriate chambers of the heart in arterial hypertension, valvular defects, etc., thus becomes clear.

From such compensatory dilatation, some investigators have endeavored to differentiate another variety, in which the elongation of the muscle fibers is a passive stretching. The conception is that although the work confronting the heart is not increased, the muscle gives way as a result of diminished contractility or tonus resulting from myocarditis, deficient blood supply, etc. This is the so-called myogenous dilatation. But even in such instances it would seem well to consider whether the dilatation is not to be viewed as compensatory. For it may well be that a functionally damaged heart muscle can meet a given load only by dilating as would a healthy myocardium under conditions demanding much more mechanical work. In other words, the diastolic volume of a chamber of the heart required to meet a given load varies inversely with the functional efficiency of the muscle.

#### HYPERTROPHY OF THE HEART

Dilatation is thus a compensatory process. It is, however, only the first line of defense of a chamber of the heart when called upon for increased work; after a longer or shorter time, dilatation is reinforced by hypertrophy. That dilatation precedes hypertrophy is obvious in the large majority of instances, and is probably always the case. This is well illustrated in acute glomerulonephritis with hypertension. In the

greater proportion of those who succumb in the first weeks, most often to acute failure of the left ventricle with pulmonary edema, the left ventricle is found dilated but not hypertrophied. On the other hand, when the duration of the disease is measured in months, hypertrophy is almost always present. Kindred observations have been made in experimental valvular lesions. The intimate association of hypertrophy with dilatation is well brought out by the observations of Kirch,<sup>3</sup> who found that both dilatation and hypertrophy are initiated in the outflow tract of the ventricle with only subsequent involvement of the inflow tract. The recent detailed studies of Gross and Kugel (personal communication) have afforded results similar to those of Kirch.

What is the link that connects hypertrophy with antecedent dilatation? This is not entirely clear, but the utility of the process is elucidated by the following considerations: Inasmuch as the volume of a sphere is proportional to the cube of the radius, as a sphere increases in size equal increments in volume correspond to smaller and smaller increases in radius. In other words, the larger a cardiac chamber, the less its radius must be diminished to expel the same volume of blood. Thus the fibers of the dilated heart contract a shorter distance in maintaining the same stroke volume than do those of the normal organ. But the force of contraction must be correspondingly greater. *Dilatation thus leads to the necessity for a shorter but more powerful contraction of the muscle fibers, and hypertrophy would seem to be the adaptation to these altered conditions.* Of course, such a line of thought merely considers the wherefore and not the how of the process by which hypertrophy occurs in the dilated heart.

#### INCREASE IN RATE

In the majority of instances, though not invariably, the rate of the failing heart is increased. Within limits, acceleration of the heart fulfills a compensatory function. Henderson<sup>4</sup> found in the dog that the minute volume increases with the rate of the heart to about 120 beats per minute, is relatively constant between 120 and 240, and falls above the latter rate. The conditions for the development of a compensatory action by tachycardia are especially favorable in cardiac failure, for the shortening of diastole that accompanies tachycardia is neutralized to a large extent by the increased venous pressure, which accelerates diastolic filling. On the other hand, in auricular fibrillation the loss of the filling quota due to auricular systole militates against compensation by tachycardia. Similarly, the low venous pressure of patients in shock prevents tachycardia from notably increasing the output of the heart. The cases in which tachycardia is so rapid as to diminish the output of the heart will be discussed later.

The pathogenesis of tachycardia in cardiac weakness has not been entirely elucidated. It is not an intrinsic adaptation of the heart to

increased work, for Starling found in the heart-lung preparation that within wide limits increments in arterial resistance or venous inflow do not affect the rate. A factor that may be significant is the Bainbridge reflex. Bainbridge<sup>5</sup> found that increased pressure within the venae cavae close to the heart and the right auricle induces reflex acceleration in rate. It has also been found that similar tachycardia results from elevation of pressure within the pulmonary veins and left auricle. The increased pressure behind a failing chamber of the heart may thus initiate compensatory tachycardia. In those instances in which cardiac failure is accompanied by fall in arterial pressure, of which coronary occlusion is an outstanding example, reflexes initiated in the carotid sinus and aorta may also play a part in accelerating the heart.

#### THE CARDINAL CIRCULATORY SYNDROMES

In any attempt to analyze the clinical pictures of circulatory failure from the point of view of the underlying disturbances in the dynamics of the circulation, the primary and obvious distinction is between failure of cardiac and of peripheral origin. In the vast majority of instances, this differentiation is readily carried out at the bedside.

In the category of cardiac failure, further classification on a dynamic basis is often feasible. In certain cases, the cardiac failure is obviously a result of interference with diastole, either in consequence of mechanical incarceration of the heart or because of undue shortening of diastole in tachycardia. The term *diastolic insufficiency* may be used to designate such instances. Far more common is the cardiac insufficiency in which there is no hindrance to diastolic filling but in which contractility is inadequate. Such *systolic insufficiency* may involve the entire heart or may be confined to the right or the left ventricle, while the other chamber is functionally efficient—right or left ventricular failure.

It is doubtless also true that different mechanisms lead to circulatory insufficiency of peripheral origin, but as yet it scarcely seems feasible for the clinician to separate them. Common to these *peripheral insufficiencies* is stagnation of blood in one or another vascular territory so that the venous return to the heart is inadequate.

Tentatively, then, we may recognize the following cardinal circulatory syndromes:

##### 1. Cardiac Insufficiencies:

###### A. Systolic insufficiency—impaired contractility.

- a. Failure of the left ventricle.
- b. Failure of the right ventricle.

###### B. Diastolic insufficiencies—inadequate diastolic filling.

- a. Mechanical incarceration of the heart.
- b. Abbreviation of diastole by tachycardia.

##### 2. Peripheral insufficiencies—deficient venous return to the heart.

##### 3. Combinations of the above.

## FAILURE OF THE LEFT VENTRICLE

Failure of the left ventricle occurs in the diseases in which the work of this chamber is increased or its muscle diseased. Hence, it is seen most often in arterial hypertension, disease of the aortic valve, and stenosis of the mouth or the trunk of the left coronary artery. Classical left ventricular failure may appear in acute glomerulonephritis, and is the chief danger in the first days of the disease. It also occurs in mitral disease with predominant regurgitation; when there is marked stenosis also, left ventricular insufficiency is unusual.

*The clinical picture of isolated insufficiency of the left ventricle is characterized by symptoms and signs attributable to increased tension in the pulmonary circuit in the presence of normal pressure in the systemic veins.*

The outstanding symptom is dyspnea. In almost every instance there is breathlessness on exertion. Often, however, the dominant type of dyspnea is paroxysmal, with especial tendency to occur at night, waking the patient in the first hours of his sleep—so-called cardiac asthma. In fact, the sole complaint may be of such nocturnal attacks of cardiac asthma. While questioning and examination almost always reveal that these patients are short of breath on climbing stairs or on other exertion, their way of life may be such that exertional dyspnea does not trouble them and that they suffer only from the nocturnal paroxysms. In the most severe of such attacks there may be acute pulmonary edema with its pink, frothy sputum. The pulmonary stasis often leads also to hemoptysis, usually only streaked sputum but occasionally copious.

Objectively, an interesting and important sign of the hypertension of the lesser circulation, as Moschowitz<sup>6</sup> has termed it, is the accentuation of the second pulmonic sound. This is of especial significance in the presence of arterial hypertension. If the left heart of the hypertensive patient is adequate, the second sound is louder in the aortic than in the pulmonic area. But with failure of the left ventricle, the pulmonic second sound becomes accentuated. In such cases, I have often heard the second sound much louder in the pulmonic than in the aortic area despite a diastolic pressure of 120 mm. or higher. It is particularly significant when, in a patient with arterial hypertension whose aortic second sound has been the louder, the pulmonic second sound becomes the more intense under observation; this is excellent evidence of failure of the left ventricle. In acute glomerulonephritis, accentuation of the second sound in the pulmonic area, generally accompanied by gallop rhythm, warns of grave danger of left ventricular failure.

The negative feature characterizing isolated insufficiency of the left ventricle is the absence of engorgement of the systemic veins and liver. Measurement of the venous pressure reveals it within normal limits; I have often found the venous pressure but 5 or 8 cm. of water despite the presence of orthopnea. Since venous pressure is normal, edema is, of

course, absent. However, the patient may be cyanotic—usually a grayish cyanosis. In many cases the cyanosis is of pulmonary origin, for the warm hands show that the blood flow is not notably retarded. In other instances, to be sure, the cold extremities testify that slowing of blood flow also plays a part in the production of the cyanosis.

There is no constancy about the height of the arterial pressure. With severe coronary artery disease, particularly if there has been thrombosis of a large branch, previous hypertension may be reduced, even to below normal values. In other patients, despite severe orthopnea and other evidences of weakness of the left ventricle, the arterial pressure is maintained at a high level. During attacks of pulmonary edema, the pressure may rise strikingly, evidently a manifestation of the asphyxia.

It should be observed that the stage of isolated insufficiency of the left ventricle may last for years in patients with hypertension or coronary sclerosis, though more often signs of insufficiency of the right ventricle are soon superadded if the patient does not improve or succumb. I have seen isolated insufficiency of the left ventricle in severe form lasting over three years. In one patient at present under observation, it seems to have been present for eight years. In such cases, almost the only complaint is dyspnea, particularly paroxysmal nocturnal dyspnea. The patients are often afraid to go to sleep because of the nocturnal attacks. Not rarely, they are considered to suffer from bronchial asthma; I made this mistake recently. Sometimes, they go through repeated tests for hypersensitiveness. Some succumb to coronary thrombosis or other accidents while in the stage of isolated failure of the left ventricle, but more often the right heart sooner or later also gives way. It is an old observation that the dyspnea of such patients may be greatly relieved when the right heart fails, with swelling of the liver and feet; obviously, this is a result of the relief of the hypertension of the pulmonary circuit.

In mitral stenosis a disturbance in circulatory dynamics akin to that of left ventricular failure, and dominated entirely by the increased tension in the pulmonary circuit, may be present for years. The outstanding symptoms are exertional dyspnea and often recurrent blood spitting; but, contrary to left ventricular failure, nocturnal paroxysmal dyspnea is rare. As long as the right heart is adequate, increase of venous pressure and its consequences are absent. Such cases present the picture of *failure of the left auricle*.

#### FAILURE OF THE RIGHT VENTRICLE

The conditions in which failure of the right ventricle occurs are those which give rise to prolonged increase of tension in the pulmonary circuit, i.e., mitral disease, emphysema, various forms of pulmonary fibrosis, kyphoscoliosis, extensive pleural adhesions and effusions, the rare forms of disease of the pulmonary artery described by Ayerza, etc. Unusual



causes are organic changes in the pulmonary and tricuspid valves and disease of the right coronary artery. Most patients with left heart failure ultimately also develop insufficiency of the right ventricle, the manifestations of which then dominate the clinical picture. Such superimposition of right ventricular failure on insufficiency of the left heart often occurs under our eyes.

Failure of the right ventricle is, of course, manifested by engorgement of the systemic veins. In the vast majority of cases, this is documented by increase in venous pressure. I have, however, seen instances of this variety in which the venous pressure was not definitely abnormal, although the liver was enlarged and tender. But if the failure be not transitory, increase in venous pressure generally soon becomes demonstrable. In severe failure of the right heart, the venous pressure may rise to great heights; tensions well above 30 cm. of water are not uncommon. This rise in venous pressure, in addition to its deleterious consequences, may also fulfill a compensatory function. Since the energy unleashed by ventricular systole is proportional to diastolic filling, it is obvious that increased venous pressure with its resultant promotion of diastolic filling will tend to elevate the work done by the right heart. Moreover, increased venous pressure tends to accelerate the heart by the Bainbridge reflex. These two effects of increase in venous pressure are synergistic, for acceleration of the heart is effective in increasing output only if filling is accomplished with sufficient rapidity.

Palpable enlargement of the liver almost always accompanies the rise in venous pressure. The engorgement of the liver may also serve a compensatory function. It is generally believed that the increased abdominal tension during inspiration plays a part in the diastolic filling of the right heart, one factor being the squeezing out of the liver like a sponge. If the liver is engorged, the amount of blood thus squeezed out is presumably greater and so increases the diastolic filling of the right heart. The amount of blood that can be squeezed out of a congested liver is readily visualized by observing the swelling of the veins of the neck that accompanies manual compression of the acutely congested organ.

Cyanosis and dyspnea are almost always present. As a rule, however, in contradistinction to failure of the left ventricle, the cyanosis is relatively much more intense than the dyspnea. In fact, in many very severe instances of right heart failure with greatly increased venous pressure and extreme cyanosis, the patient does not volunteer dyspnea among his complaints and lies flat without any indication of orthopnea. The combination of engorged veins and deep cyanosis in the absence of striking dyspnea immediately suggests failure of the right heart.

In many instances, the cause of the disproportionately severe cyanosis is arterial anoxemia due to the pulmonary lesions primarily responsible for the strain on the right heart. But with severe failure the cyanosis

is not entirely pulmonary in origin; the cold extremities often indicate that slowing of the blood flow in the periphery with consequent increased reduction of oxyhemoglobin also plays a part. In addition, the polycythemia often present in these patients facilitates the appearance of cyanosis. A further factor has been emphasized by Uhlenbruck,<sup>7</sup> who has shown by experiments with inhalation of low concentrations of oxygen and high percentages of carbon dioxide that the irritability of the respiratory center in such patients with chronic arterial anoxemia is diminished. The condition of the patients is analogous in this respect to morphine intoxication, in which there is also deep cyanosis in the absence of dyspnea.

Another symptom of the more severe of these cases that has impressed clinicians is somnolence; I have seen stupor persist for days and weeks. This is presumably also a consequence of protracted oxygen want.

That edema and serous effusions may attain prodigious extent in these patients with high venous pressure need scarcely be mentioned.

I should like to refer briefly to the unusual instances of right ventricular failure resulting from disease of the right coronary artery. Such cases may run a chronic course with cyanosis, edema, serous effusions, and a large, hard liver, thus simulating Pick's disease. Dyspnea may be but slight and orthopnea absent. In a patient with this clinical picture who came to necropsy recently, paracentesis of the abdomen had been necessary four years before death and cardiac cirrhosis had developed. The picture of disease of the right coronary artery with acute failure of the right heart may be very striking. Such a case was recognized *intra vitam* by Dr. E. Libman by the concomitance of rapid and massive enlargement of the liver with the development of sinoauricular block.\*

#### CARDIAC FAILURE DUE TO INADEQUATE DIASTOLIC FILLING

Interference with diastolic filling entails corresponding diminution in systolic output. Such inadequate diastolic filling may result from either limitation of diastolic relaxation or the abbreviation of diastole in excessive tachycardia.

The classical example of cardiac failure due to mechanical limitation of diastole is furnished by rapidly accumulating pericardial effusion. Cohnheim<sup>10</sup> long ago observed that when the pressure in the peri-

\*The great significance of the venous pressure for the clinician has been repeatedly indicated in the foregoing. Nevertheless, measurements of venous pressure have not been widely applied in clinical work because of difficulties in carrying out the measurement. In a recent lecture, Lewis<sup>8</sup> has described in masterly fashion the rough estimation of the venous pressure by observation of the height of the blood column in the superficial veins of the neck. A very simple and apparently adequate method for the direct measurement of venous pressure has been introduced by Taylor, Thomas and Schleiter,<sup>9</sup> which I have found very useful. Using this method, the venous pressure in healthy individuals is between 4 and 8 cm. of water, rarely reaching 10 cm. Indications of the progress of patients with failure of the right heart can be obtained from the venous pressure. Thus, I have often seen successful digitalization in mitral stenosis with auricular fibrillation result within forty-eight hours in a fall in venous pressure from about 25 cm. of water to the normal level of about 6 cm.

cardial sac of a dog is raised by the injection of fluid, aortic pressure falls concomitantly with rise in venous pressure. Precisely the same phenomena are observed in copious pericardial effusion in man if it is formed with sufficient rapidity. That the mechanical limitation of diastole by the compressing fluid causes the cardiac failure is proved by the immediate relief that follows paracentesis. In a recent instance of purulent pericardial effusion with low arterial and high venous pressure, the physician taking the pulse could feel the hands become warmer as the pulse strengthened during the course of the paracentesis.

An analogous variety of cardiac failure resulting from limitation of diastole is encountered in thickening of the pericardium in which the contracting scar tissue incarcerates the heart, the Pick syndrome. Volhard<sup>11</sup> has described cases of this type in which the contraction of the thickened pericardium was so marked as to result in a small cardiac silhouette; when the heart was freed surgically, the patient improved. The syndrome has been reproduced experimentally by Beck,<sup>12</sup> who has shown in both animals and man that when the heart is freed from the incarcerating scar tissue which interferes with diastolic relaxation and may compromise the mouths of the venae cavae, venous pressure falls and cardiac output rises to normal.

The other type of cardiac failure due to inadequate diastolic filling results from shortening of diastole in tachycardia. The clearest example is the cardiac failure with rise in venous pressure and swelling of the liver that occurs in some episodes of paroxysmal tachycardia. Barcroft, Bock and Roughton<sup>13</sup> demonstrated in such a case that the minute volume was decreased during the attack.

The clinical picture of diastolic failure closely resembles that of insufficiency of the right ventricle, despite the fact that the filling of both ventricles is interfered with. The explanation is probably that the output of the right ventricle is so small that the left ventricle, despite equally severe functional impairment, is able to master it and thus avert the pulmonary engorgement which produces the characteristic symptoms of left ventricular failure. However, the diminution in output of the left ventricle may result in fainting and other manifestations attributable to cerebral anemia; these occur especially in the diastolic failure of paroxysmal tachycardia. In instances of copious pericardial effusion, features of both right and left ventricular insufficiency may be commingled. In such cases, the mechanical conditions may be such as to interfere relatively more with the filling of the left heart and thus result in pulmonary engorgement and agonizing dyspnea.

#### CIRCULATORY FAILURE OF PERIPHERAL ORIGIN

Since the capacity of the vascular tree is far greater than the volume of the blood, simultaneous relaxation of all the vessels would be incompatible with the maintenance of circulation. Variations in tonus of the

arterioles in different vascular territories guide the blood to the organs where it is needed. The capillaries also participate in the regulation of blood distribution; classical examples are the increase in the number of open capillaries in active muscle and the changes in the proportion of permeable glomerular loops as diuresis varies. Henderson,<sup>14</sup> Gollwitzer-Meier<sup>15</sup> and others have emphasized the importance of alterations in the capacity of the veins for the regulation of the circulation. This is of particular significance because the capacity of the venous side of the circulation is several times that of the arterial. The conception advocated by Hess<sup>16</sup> is that the arterioles serve to regulate the distribution of blood among the various organs while the veins are preponderant in regulating the total volume of the circulation. Diminution in the capacity of the veins immediately increases the return to the heart and therefore the output of that organ. Accessory factors of significance in aiding the venous return to the heart are contraction of the skeletal muscles and the respiratory movements; how strikingly muscular activity aids venous return to the heart is obvious when one asks a patient to clench his fist during venipuncture.

Evidently, a mechanism so elaborate as that regulating the distribution among the organs and the return to the heart of the blood must have a variegated pathology of its own. The classical example of such a circulatory disturbance originating in the periphery is surgical and traumatic shock. Peripheral factors are probably likewise dominant in the genesis of circulatory failure in many of the acute fevers, although in some of these, notably rheumatic fever and diphtheria, damage to the heart muscle plays a part or is predominant. The circulatory collapse that is now the chief danger in diabetic acidosis is also of this variety. Experimentally, circulatory failure of peripheral origin can be produced with histamine.

In each of these varied conditions, there appears to be stagnation of blood in the vascular periphery with resultant diminution in the venous return to the heart. That the pooling of blood in the periphery of the circulation is not due to cardiac weakness but is of peripheral genesis is proved by the low pressure in the large veins of the extremities. Even though the heart is functionally competent, the small return from the great veins entails an equally diminished cardiac output; hence the fall in arterial pressure, to which arteriolar dilatation may also contribute. The low arterial pressure in turn accelerates the heart through reflexes originating in the carotid sinus and aorta. The circulatory disturbance resulting from diminished venous return is one for which the heart cannot compensate. The reason for this is that filling is an entirely passive process on the part of the heart, which functions solely as a force pump, it does not, like a suction pump, aspirate blood from the venae cavae.

As to the causes of the stagnation of blood in the periphery, there are many theories but few established facts. The following mechanisms seem the best grounded:

1. It is widely held that the peripheral stasis is due to increased capacity of the small vessels, particularly in the splanchnic area, resulting from diminution in their tonus. Formerly, the stagnation was thought to be chiefly in the capillaries, but some recent investigators tend toward the view that most of the pooling of blood occurs in the very capacious venules. In the case of arteriolar relaxation, the actual increase in the capacity of the arterioles is probably not as significant as is what we may term the "guiding function" of the arterioles, i.e., the blood is no longer guided effectively to the active organs in which it is needed by the tonic contraction of the arterioles in the inactive parts.

2. Henderson<sup>14</sup> has for years defended the thesis that the peripheral stasis is due to diminished venous return to the heart—defective function of what he terms the venopressor mechanism—so that the blood stagnates in the venules. In Henderson's opinion, deficiency of carbon dioxide in the blood and tissues results in diminished tonus of the muscles and depresses respiration; when the venous return to the heart is deprived of these aids, peripheral stagnation is favored.

3. A number of investigators have found diminished circulating blood volume in peripheral circulatory failure. In some instances, such as diabetic coma or postoperative vomiting, this is at least partly due to concentration of the blood by dehydration. But in other cases the decrease in the volume of the circulating blood is believed to be caused by removal of blood from the rapid circulation into the various blood reservoirs, such as the spleen and the liver. This conception has been advanced especially by Eppinger.<sup>17</sup> It does not seem to me that the significance of the diminution in circulating blood volume associated with peripheral circulatory failure is as yet elucidated.

Considering the complexity of the mechanisms involved in the peripheral circulation, it would seem probable that there are various pathogenetically distinct types of peripheral circulatory failure, having in common stagnation of blood in one or another vascular territory and diminished venous return to the heart. But the means for differentiating these varieties are not yet at hand, and the clinician must be content with the separation of the circulatory failures of peripheral genesis from those due to cardiac weakness.

Before leaving the subject of peripheral circulatory failure, it would seem worthy of emphasis that both cardiac and peripheral failures may occur simultaneously. Thus, in cases of coronary thrombosis, the element of peripheral failure is often prominent and may completely dominate the clinical picture for a time. In such instances, although there is ashy cyanosis and the extremities are cold, I have repeatedly

found the venous pressure to be low. Despite a large infarct in the left ventricle, there may be no evidence of pulmonary congestion for a considerable time; the pulmonic second sound is not accentuated and the patient lies flat on his back without orthopnea. Evidently, so much blood is pooled in the periphery that the venous return is small enough to be within the capabilities, for a time at least, of even the severely damaged heart. Possibly, such cases are to be included in the concept of traumatic shock, the infarction of the myocardium being the responsible trauma. But the possibility must also be weighed whether the peripheral pooling of the blood is not a protective measure—effected through as yet unknown mechanisms—to relieve the acutely damaged heart.

Therapeutic considerations have not been broached in the foregoing discussion. That the treatment of circulatory failure of peripheral origin differs fundamentally from that of cardiac failure is, of course, well known. But I believe it has not been adequately emphasized that the therapeutics of the various types of cardiac failure must be individualized in accord with the nature of the disturbance in the dynamics of the circulation. Time will permit only one illustration of the importance of such therapeutic individualization: The sovereign domain of digitalis is failure of the right heart; I have convinced myself by protracted observation that it is rarely efficacious in isolated insufficiency of the left heart or in diastolic insufficiency. That is, it has not seemed to me that the results obtained by digitalization in isolated failure of the left ventricle by digitalization are superior to those observed by bed rest, fluid and salt restriction, and perhaps the administration of salyrgan without the additional use of digitalis. The difference is not entirely explained by the fact that auricular fibrillation occurs predominately with right heart failure, for there may be excellent therapeutic response to digitalization in this type of failure with regular rhythm. Whatever the explanation may be, much unnecessary digitalization will be avoided by realization that the sphere of usefulness *par excellence* of digitalis is insufficiency of the right heart, and that when the drug fails in other varieties of cardiac insufficiency, the only effect of increasing the dose is liable to be intoxication. The relation of the type of cardiac failure to the therapeutic response would seem worthy of more study than has hitherto been accorded it.

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## CLINICAL ASPECTS OF ARTERIOSCLEROSIS\*

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THIS discussion of human arteriosclerosis is undertaken with a certain unwillingness, because as every student of the subject must appreciate, our ignorance of this very common affection far overshadows our knowledge. A search of past writings for established fact leads to disappointment; hypotheses there are in abundance, but these frequently express opposite views concerning the cause and nature of arteriosclerosis.

For the purpose of this discussion I exclude those changes in the arteries due to syphilis, tuberculosis, trauma, toxic agents leading to thrombosis, and that rather rare inflammatory process, periarteritis nodosa. With less justification perhaps I exclude also the medial necrosis and calcification of peripheral vessels, described by Mönckeberg. I shall use the older and better known term "arteriosclerosis" introduced by Lobstein to denote that most common affection of the arterial system, of undetermined etiology, rarely absent in advanced life, and characterized by a thickening of the intima accompanied by the deposition of fat. Changes in the media are usually mild, although in some instances they are marked. Later sclerosis and calcification occur, which give to the arteriosclerotic artery its most characteristic appearance.

To enter upon a discussion here of the anatomical changes in arteriosclerosis would carry us far afield and would be productive of nothing new. Whether the process is primarily in the intima or in the media, or whether it is inflammatory or degenerative in nature is not settled. Klotz<sup>1</sup> thinks that the sclerotic changes in the vessels are due for the most part to intimal disease caused by infectious processes, work and old age, while MacCallum<sup>2</sup> has stated that the media in the aorta and visceral arteries seems relatively little changed in comparison to the extent of the intimal alterations. Included here are those changes in the smaller ramifications of the vascular tree known as arteriolar sclerosis. No attempt is made to differentiate this process from arterial sclerosis because the two are very frequently associated, and so far as we now know they may have a common pathogenesis.

Arteriolar sclerosis affecting arterioles of the order of the vasa afferentia in the kidneys is characterized by the irregular deposition of hyalin under the endothelium as seen best in longitudinal sections of

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the arteriole. Such hyalinized areas may undergo a fatty change which can be demonstrated by lipoid stains such as sudan III. As the process advances the lumen of the vessel is narrowed or completely obliterated. In larger arterioles one sees only the hyperplastic type of intimal thickening with retrogressive and fatty changes and later proliferation of connective tissue. Often in advanced cases the media shows degenerative changes with complete replacement fibrosis. Medial hypertrophy of the kidney arterioles is seen particularly in individuals under forty dying of hypertension.

Reviewing the present day conceptions of the etiology and pathogenesis of arteriosclerosis, one finds much speculation and many hypotheses often masking as fact. In a review of the subject in 1922, MacCallum<sup>2</sup> stated: "Arteriosclerosis is one of those diseases difficult to explain because it develops so slowly through long years of life, during which a great many possible causes have had an opportunity to affect the tissues. Hence every conceivable idea has been expressed or tenaciously maintained regarding the condition and many of them are so vague and ill supported that it is wearisome to discuss them. None, however, is clearly demonstrated to have a definite bearing on the etiology of arteriosclerosis and we are quite as ignorant of its underlying causes as were our fathers in the days of Morgagni."

Aware of the truth expressed in this quotation of MacCallum, we find it difficult, however, to dismiss summarily from consideration certain factors which have long been thought to be of some significance in the cause of human arteriosclerosis. I refer to the influences of heredity, to the ravages of the ageing process, to hypertension, and to those changes in our environment incident to our civilization, not because these are in any sense all the factors that may be involved, but the evidence in their favor is perhaps open to less criticism than that presented by other alleged etiological agents.

#### INCIDENCE OF ARTERIOSCLEROSIS

Accurate data on the present incidence of arteriosclerosis are not available, but indirectly, certain more or less pertinent facts are obtained by a study of mortality and morbidity statistics. These show for the registration area in America, first, that heart disease is the leading cause of death at present and, second, that the mounting incidence of heart disease during the past two decades occurs in individuals past forty years of age. For example, heart disease in the state of New York, excluding New York City, has been the leading cause of death since 1912 with the exception of the year 1918 when pneumonia held first place. The curves show an almost continuous rise from a rate of 133.5 in 1900 to 279.9 in 1928, when 50.6 per cent of the deaths were between the ages of forty and seventy, and only 8.3 per cent of deaths from heart disease were under forty years of age.

Assuming a certain error inherent in such data, there is little reason to doubt the statement that the most significant factors in heart disease beyond forty are vascular decay, coronary arteriosclerosis, and those changes in the smaller arterioles that we know are so frequently associated with hypertension. If, in addition, we add that group of individuals beyond forty who die of cerebral arteriosclerosis (thrombosis or hemorrhage) and those dying of renal insufficiency secondary to vascular disease, it is apparent that at the present time the expectancy of life of the majority of people beyond middle age is determined by the state of the arteries. Long ago it was said "A man is as old as his arteries." This truth is even more apparent today than ever before.

Much attention is given in some quarters to the steadily mounting morbidity and mortality rates from cardiovascular disease, and a variety of opinions is expressed concerning their significance; but before any definite conclusions are reached, it is necessary to know much more than we do at present concerning many factors that appear to influence the incidence of arteriosclerotic changes in vessels.

Data on the life span show that there are today in this country more people fifty years of age than ever before. Only a few decades ago the age at which most people died was 45; now it is 60. The control of some of the important causes of death in infancy and childhood has increased the number of people past middle life—in the arteriosclerotic age—hence a certain natural increment in the incidence of vascular disease is to be anticipated. Furthermore, modern hygiene and preventive medicine are striving daily to increase the number of individuals (both fit and unfit) that mature to approach the involutionary period of senescence. Man is exercising more and more control over his environment, and there are those who point with pride to his accomplishments in prolonging human life, but the biologist and the eugenicist ponder the ultimate results of our present day methods as applied to the human race. They see the waning influence of natural selection and wonder if we can continue to thwart nature without paying the penalty in quality if not ultimately in quantity. In fact, there is some reason to believe that nature is already exacting her toll. Professor Forsyth<sup>3</sup> of Dartmouth has presented evidence to show that the length of life in this country is actually decreasing. From a critical analysis of mortality statistics he concludes that the American adult today cannot expect to live as long as his father or grandfather. There is little question that many individuals today are maturing to propagate the race who would not have survived in the more rigorous environment of our forefathers. If the wearing quality of our arteries is in any way determined by our heredity (a point emphasized by the late Dr. Osler), may we not expect an increasing number of people whose vessels may wear reasonably well for the earlier decades of life but as age comes on the shoddy appears in the form of early deterio-

ration of the vascular system. It appears that this view, admittedly difficult either to prove or disprove, cannot in the light of our present knowledge be summarily dismissed as sheer speculation.

#### CLINICAL ASPECTS OF ARTERIOSCLEROSIS

Although we are far from a solution of the problem of the pathogenesis of human arteriosclerosis, valuable contributions to our knowledge have been made by both pathologists and clinicians in the days since Bright. Time will not permit a discussion of the voluminous literature that has grown up on the subject in the past century, but it is necessary to mention the contributions of a few workers who have been most responsible for our present day conceptions. These are not perfect and they are slowly changing, but there is little doubt that the informed clinician at present is much better equipped than were his predecessors of the past generation to appreciate the variety of clinical conditions either associated with or directly due to arteriosclerotic changes in the vascular tree.

Knowing as we now do the frequent association of hypertension and left ventricular hypertrophy with sclerotic changes in the intimate vasculature of several organs—most often the kidneys—it is not surprising that the early students of kidney disease should have been concerned also with the problem of vascular disease. Bright<sup>4</sup> observed the occurrence of thickened vessels and cardiac hypertrophy in patients with contracted kidneys, but he had no clear conception of the causal relation. To understand the origin of the term "Bright's disease" and "Bright's kidneys" and to appreciate the influence that these terms have had on moulding our views even to the present time, we should recall that Bright's work dealt with no particular form of renal disease but included all cases with an albuminous urine during life and a scarred kidney postmortem. Kidney lesions were no further classified by Bright than as "large and smooth" and "small and granular," exceptions being regarded as intermediate stages in the process of development from the large to the small kidney. Originally, therefore, the term Bright's kidney included many forms of renal disease. It is interesting to note that following Bright's work and persisting for many years were certain conceptions regarding kidney disease which have done more to retard than to advance our knowledge. Chief of these were: First, that all types of scarred kidneys were manifestations of one disease process at different stages; and, second, that the associated lesions of other organs, such as those of the heart and arteries, were the effects of renal disease and due to progressive renal insufficiency.

It was not until some twenty years after Bright that the vascular lesions associated with renal disease received much attention. In 1852 Johnson<sup>5</sup> showed that in one form of chronic Bright's disease the

smaller arteries not alone in the kidneys but also in other viscera were thickened—changes which he ascribed to antecedent renal disease. The contribution which marked an epoch in our knowledge of vascular disease was that of Gull and Sutton<sup>6</sup> in 1872. They confirmed Johnson's observations but took an important step forward by showing that a diffuse vascular disease of the smaller vessels (arteriocalillary fibrosis) may occur without serious renal damage. They further suggested that left ventricular hypertrophy was due to the change in the minute arteries and capillaries and not to renal insufficiency. The observations and deductions of Gull and Sutton are all the more remarkable when we recall that they were made with imperfect histological methods and with no knowledge of clinical blood pressure. As conclusive as their work appeared, it was not a death blow to the older conceptions of the dependence of cardiac hypertrophy and arteriosclerosis upon renal disease.

About twenty years after the work of Gull and Sutton, the sphygmomanometer was introduced into clinical medicine by von Basch. As clinical data on blood pressure gradually accumulated, it was but natural that some association between abnormal elevations in blood pressure and sclerotic changes in vessels should be postulated, and supporting evidence for this view was afforded by those incidences of hypertension associated with demonstrable sclerosis of the accessible arteries. However, exceptions to the rule were not long in appearing. Von Basch in 1893,<sup>7</sup> after observing many cases of hypertension without demonstrable arterial changes, concluded that the hypertension was but a precursor of arteriosclerosis, and to designate such conditions he used the term "latent arteriosclerosis." Still lurking in the background now more than twenty years after Gull and Sutton's work, and more or less dominating the clinical thought of the time was the old teaching concerning the unity of arteriosclerosis and kidney disease. To bring the earlier observations on blood pressure into line with this view, it was taught that hypertension was a manifestation of arterial change which in turn resulted from renal disease. Therefore individuals with an abnormal elevation in blood pressure were regarded as having, or destined to develop Bright's disease and renal insufficiency. Such was the generally accepted and almost universally taught hypothesis concerning the relationship between arteriosclerosis, blood pressure, and kidney disease, in the early 90's of the last century.

In retrospect we may say that the stage was set for recognition of that large group of individuals with chronic hypertension who never develop renal insufficiency, and who have no significant changes in the palpable arteries. For this step forward we are indebted to Allbutt, although about the same time Huchard<sup>8</sup> in France was aware of the frequency of nonrenal hypertension. Long and careful observations on

patients led Allbutt<sup>9</sup> to the following well known classification: (1) hyperpiesia—individuals with chronic hypertension with little or no renal involvement who die of heart failure or apoplexy; (2) renal disease with or without hypertension; (3) decreescent arteriosclerosis, primarily of the larger arteries, not necessarily accompanied by hypertension. In his zeal to stress the importance of hyperpiesia and to have it regarded as a distinct malady, Allbutt failed to recognize, or at all events did not include in his classification, those cases of primary hypertension that die of renal insufficiency. Such cases have until very recently presented a barrier to any classification of nephritis; they have led to no little confusion between clinicians and pathologists and have helped to keep alive the old conceptions of the renal origin of hypertension.

After Gull and Sutton, the most outstanding contribution from the pathological standpoint was made by Jores<sup>10</sup> in 1904, who showed for the first time that the scarred kidney, formerly regarded as the seat of chronic interstitial nephritis, was in reality due to arteriosclerosis of the smaller renal vessels. He further observed<sup>11</sup> that patients with atrophic granular kidneys had hypertrophied left ventricles, and more often died of cardiac failure or apoplexy. Jores' work supported that of Allbutt and served to emphasize the view that cardiac hypertrophy and hypertension were not due to renal involvement. Opponents on the other hand supported their argument by citing cases of hypertension that died of uremia. For several years following the work of Allbutt and Jores clinicians generally, recognized that some relationship existed between arteriosclerosis, hypertension, cardiac hypertrophy and granular kidneys, but, as most of us recall, the teaching of twenty years ago was anything but clarifying. The diagnosis of cardiovascular renal disease was commonly made, but so far as the student was concerned, just what part of the clinical picture was due to cardiac failure and what to renal insufficiency was seldom determined with any degree of accuracy. Retained body fluid and an albuminous urine were usually sufficient evidence to incriminate the kidneys.

The clear recognition of two types of primary hypertension, one with renal insufficiency, the other without, and the corresponding vascular renal lesions were established by Volhard and Fahr<sup>12</sup> in 1914. Thus for the first time the hitherto puzzling case of hypertension and renal insufficiency was brought into line, but not without an argument among pathologists which has continued to the present time. This arose from the assumption by Volhard and Fahr that the kidney lesions, particularly in the glomeruli, in their cases of so-called malignant hypertension dying of renal insufficiency, were not due solely to vascular damage but were a combination of vessel and inflammatory renal changes, their *Kombinationen*—Form. Both authors have now changed their original views, Volhard<sup>13</sup> holding that the vascular renal

lesions are ischemic in nature, the result of vascular spasm. This phase of the subject is presented in a recent contribution of Klemperer and Otani,<sup>14</sup> who distinguished two types of vascular lesions, one a rapidly progressive atherosclerosis, the other, an inflammatory lesion superimposed on an antecedent arteriosclerosis.

The above brief resume of a few of the more important contributions since Bright, gives us a glimpse of the development of our present knowledge concerning the relationship of arteriosclerosis, hypertension and certain forms of kidney disease, and it also indicates the difficulties encountered in the past in correlating clinical and pathological observations. That our present knowledge is immature is apparent to all, but may not its abundant heritage promise much for the future?

Before attempting what we may call a pathological-physiological classification of arteriosclerosis, certain well known facts may be emphasized: First, that those changes in the arterial tree that we call arteriosclerosis are most capricious in their distribution, appearing in the greater circulation from the sinus of Valsalva to the smallest arterioles (for some reason not known at present the arteries of the lesser circulation in most cases are singularly spared). The process may be generalized in some instances and sharply localized in others. Second, that the functional significance of arteriosclerosis varies greatly; often there is no parallelism between the extent of the process and the associated functional disturbances. For instance, we see extensive changes in the larger arteries that offer no barrier to longevity, and on the other hand, the process may be confined to a few millimeters of the coronary artery and cause sudden death in the prime of life. Serious damage to the intimate vasculature of the kidney is found in young people dying of uremia. Chronic hypertension and sanguineous apoplexy usually are associated with damaged cerebral vessels. Many other examples might be cited to illustrate the variety of clinical pictures associated more or less intimately with vascular disease. Our limited knowledge at present precludes a satisfactory classification of arteriosclerosis (this term to include both large and small vessel involvement), but since we as clinicians are primarily concerned in correlating the clinical and pathological findings, the following scheme may serve as an outline in approaching a discussion of the subject.

This outline makes no claim to perfection and it has many vulnerable spots. To perceive them is to appreciate the difficulties in associating functional disorders and anatomical changes, particularly changes so irregular in distribution as are those of arteriosclerosis. Certain quite obvious objections may be made to the association of arterial and arteriolar sclerosis and blood pressure, but in indicating a relationship between hypertension, for example, and small vessel disease, no more is implied than the fact that most individuals with so-called essential hypertension show at post-mortem examination more or less marked

propagated to the periphery, as shown by Bramwell.<sup>17</sup> More of the shock of ventricular systole is transmitted peripherally, and we find an abnormal excursion of the vessels from the aortic arch, for example the carotids. Sclerotic changes at the root of the aorta not infrequently involve the valve cusps, which become rigid, are unable to approximate the aortic wall during systole, and may lead to a high grade of aortic stenosis and death from heart failure. Incidences of aortic insufficiency ascribed to arteriosclerosis are often due to syphilis which may not be recognized grossly in the presence of advanced arteriosclerosis. Mention here may be made of an interesting anatomical finding first called to my attention by Professor Erdheim. He points out that the first few centimeters of the aorta are singularly spared in individuals who attain seventy years or more, although the remainder of the vessel is more or less extensively diseased. On the other hand, marked involvement of the first 3 to 4 centimeters appears to be incompatible with the proverbial three score and ten years. Exceptions to this rule are very rare. In searching for some explanation of this fact, one is reminded of the evidence indicating that the first part of the aorta is nourished from the coronary arteries, so that it is possible some relationship between coronary disease, at least of those branches that supply the aortic root, and sclerosis in this region exists. This matter merits further study.

The reference to combined lesions, as indicated in the right half of this diagram, is of course absolutely necessary, since several combinations of functional and anatomical changes may occur. For example, the larger arteries are almost always involved in long standing cases of hypertension and, indeed, the clinical course may be dominated entirely by the large vessel disease.

At this point I desire to present briefly the salient clinical and pathological findings in one case which illustrates the extent of the problem of vascular disease. Those of you who attended the Cleveland meeting of the American College of Physicians in 1927, will recall a boy aged twelve years whom I demonstrated as an example of juvenile nonrenal hypertension.

This boy developed normally, and except for an attack of lobar pneumonia at the age of eight years, he was in good health until eleven years of age. There was no history of rheumatic infection or scarlet fever. One year before coming under our observation he noticed undue breathlessness and palpitation while at play. He complained also during this year of rather regularly recurring attacks of severe headache. These symptoms progressed and formed the chief complaint on admission to the hospital, January 20, 1927.

Physical examination revealed a well-developed and alert boy of good color, in no distress, and with no puffiness about the face or edema elsewhere. Blindfolded, one would have said from palpation, that the accessible arteries were those of an old man. They were thickened and tortuous, and it was apparent that the blood pressure was elevated, and when measured it was found to be 280 mm. of mercury systolic, and 175 diastolic. At a glance one was impressed by the vigor and position of the

cardiac impulse, which was maximum in the sixth left intercostal space, extending almost to the anterior axillary line. At the apex the heart sounds were loud and booming, but as one approached the base a loud diastolic murmur was audible, with maximum intensity over the manubrium. In this position one also heard a snappy and tympanitic second sound followed at once by the blowing diastolic murmur. It was thought that this murmur was due to relative incompetence of the aortic valves, as it entirely disappeared when the systolic blood pressure was lowered from 280 to 190 by the administration of nitroglycerine. It is of note also that this acute drop in blood pressure always caused a severe headache.

The eyegrounds were typical of hypertensive retinitis. Neither disc was discernible from swelling of the adjacent retina. There were numerous areas of recent hemorrhage and a few whitish spots were observed. Only a few retinal arterioles were visible. These showed marked sclerosis. Further clinical study of the case revealed a normal blood picture, hemoglobin 90 per cent with 4.3 million red blood cells per cubic millimeter. The blood urea nitrogen on several occasions varied between 40 and 60 mg. per 100 c.c. The urine was pale and the specific gravity varied between 1.010 and 1.015. It always contained albumin and the sediment showed a few casts. The phthalein output was 50 per cent in two hours.

During the first month in the hospital, the symptoms complained of on admission improved, and the child appeared so well that his parents insisted upon taking him home. Two weeks later, and while at home, he developed suddenly a right-sided hemiplegia with the signs of an upper neurone lesion of the seventh nerve. Two days afterwards he was readmitted to the hospital, but no improvement in his condition occurred. His paralysis continued, he became more and more lethargic, and died April 5, two and a half months after his first admission. The anatomical diagnosis was as follows: marked generalized arteriosclerosis; arterial and arteriolar sclerosis of kidneys; cardiac hypertrophy (weight 475 grams); massive cerebral hemorrhage, left; hemorrhagic infarcts of intestines; acute splenic hyperplasia; edema of lungs. Microscopically arteriolar lesions were demonstrated in the kidneys, liver, spleen and pancreas. For the following histological description of the kidney lesions I am indebted to my colleague Dr. Harry Goldblatt. One of the striking features is the relative absence of glomerular lesions. An occasional glomerulus shows fatty degeneration or focal hyalinization of the tuft, with or without adhesion to the capsule. The most striking pathological change affects the blood vessels and especially the interlobular and afferent vessels. In the larger arterioles there is mainly thickening of the intima due to cellular proliferation. In the smallest ones the thickened, proliferated intima shows patchy or complete hyalinization with or without fatty degeneration; which shows well in sections stained with sudan III. The media of the smaller vessels is definitely hypertrophic but in most instances shows no other pathological change. The vascular lumen is in all instances reduced in size and in many of the vessels it is completely obliterated.

From the above account we see a case of extensive and severe diffuse vascular disease with hypertension and death from cerebral hemorrhage, in a boy of twelve years. Certainly we cannot invoke the ageing process, and there is little evidence that infection played an etiological rôle in the production of the vessel disease in this case.

In summary, we may say that the present day clinician sees in human arteriosclerosis a pathological process affecting the arterial system of the greater circulation from the largest to the smallest vessels, usually insidious in its onset, and most irregular in its distribution. Its pathogenesis is an unsolved problem, but in speculating we turn to



the influence of such factors as heredity, the ravages of age, hypertension, and those changes in our environment incident to modern civilization. When we know more about the causes of essential hypertension, we shall be farther on the road to the solution of the problem of arteriosclerosis, particularly the form that involves the smallest vessels, the arterioles.

We have seen that statistics indicate a mounting incidence of vascular decay, particularly in middle life, but we are reminded of the fact that individuals are living longer today than ever before, and deterioration of the arteries appears to be a favorite method of Nature to eliminate us after our biological responsibilities have been fulfilled. Complicating the problem and exerting an influence difficult to evaluate, are our present day efforts to thwart the law of natural selection.

One is reminded of the proverb, "So long as more remains to be done, nothing seems done." However, the canvas is being painted, a high light here, a shadow there, and if we are at present forced to speculate on the appearance of the final picture, we should be stimulated rather than deterred in our efforts to solve one of the most important and most perplexing problems with which the clinician and pathologist have to deal—the problem of vascular disease.

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# THE ORDER OF VENTRICULAR EXCITATION IN HUMAN BUNDLE-BRANCH BLOCK\*†

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IN previous articles from this laboratory<sup>1, 2</sup> it has been pointed out that, in accordance with the laws which govern the flow of electric currents in volume conductors, the potential variations produced by the cardiac muscle are very much greater in magnitude in the immediate neighborhood of the heart than at a distance from it. It has been shown that when one electrode of the string galvanometer is placed upon the precordium, the position of the second electrode, so long as it is distant from the heart, has comparatively little influence upon the form of the ventricular electrocardiogram. Attention has been called to certain resemblances between leads of this type‡ and direct leads of the kind employed by Lewis and Rothschild<sup>3</sup> in which one electrode is placed in actual contact with the ventricular muscle and the other upon the chest wall. In both cases the form of the ventricular complex is determined in a very large measure, although not to quite the same extent in the former as in the latter, by the potential variations of the exploring electrode; in both cases the muscle units which lie nearest this electrode exert individually a much greater effect upon its potential than those which are more distant from it.

Curves obtained by leading from points on or near the heart to one of the extremities utilized in taking the three standard indirect leads may be freed from the influence exerted by potential variations of the indifferent electrode by a method which we have recently described.<sup>4</sup> When this electrode is placed upon the left leg the correction is made by subtracting from each ordinate of the recorded curve one-third of the sum of the deflections, measured in millivolts, inscribed in Leads I and II at the corresponding instant in the cardiac cycle. It is possible in this way to determine, at least approximately, the time course of the potential of the exploring electrode, and thus to eliminate any difference between direct and semidirect leads for which potential variations of the indifferent electrode are responsible.

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†A brief preliminary report of the observations upon which this article is based appeared in the *Proc. Soc. Exper. Biol. and Med.* **27**: 586, 1930.

‡We term all indirect leads in which one electrode is placed very much closer to the heart than the other *semidirect leads*. We call the electrode which is nearer the heart the *exploring electrode*; that which is more distant, the *indifferent electrode*. We refer to semidirect leads in which the exploring electrode is placed upon the precordium as *precordial leads*.

So far as we are aware, there is no reason to believe that in direct leads of the type under consideration the exploring electrode bears any special relation to the ventricular muscle other than that of great nearness to the fibers lying just beneath it. In direct leads from the outside of the exposed heart, it is true that the exploring electrode is in contact with a surface which, if we neglect the thin epicardium and film of fluid which covers it, is bounded by a di-electric, but this factor does not seem to be an important one in determining the distinctive characteristics of the recorded curve. In leads from the endocardial surface of the heart it is not present, and Lewis and Rothschild found that flooding the pericardium with blood did not materially alter the time of the chief deflections obtained by leading from the immersed epicardial surface. Between direct and semidirect leads there can, therefore, hardly be any fundamental difference. In the latter, as compared to the former, the exploring electrode is more distant from the heart as a whole. Its distance from the nearest muscle units is absolutely greater and relatively greater in comparison with its distance from other parts of the heart. The potential of the indifferent electrode exercises a relatively larger influence in semidirect than in direct leads. Apparently, these are the only respects in which the two methods of leading differ materially. Suppose that we were to start with a direct lead and gradually move the exploring electrode away from the surface of the heart, electrical contact being maintained by surrounding heart and electrode with a medium of approximately the same specific conductivity as the body tissues. The form and amplitude of the recorded deflections must then change in a continuous manner; rapidly at first, but more gradually as the distance of the electrode from the heart increases. Since moving the exploring electrode away from the heart tends to decrease the influence exerted by the muscle units with which it was originally in contact and to increase relatively the influence of the muscle units lying adjacent to them, it is clear that when the area of cardiac surface over which similar potential variations occur simultaneously is extensive all resemblance between the deflections of the direct and those of the final semidirect lead will not be lost until the distance of the exploring electrode from the heart is comparatively great.\*

This line of thought and the character of the ventricular deflections in precordial leads led us to suspect that there might be a close relation between the form of these deflections and those which would be obtained by leading directly from the underlying portions of the ventricular wall; and consequently that, by the use of such leads, the general order of ventricular excitation in man might be determined directly. Even if this suspicion should prove unwarranted, it seemed probable that a comparison of the ventricular deflections obtained by semidirect leads in

\*The fundamental principle involved here has been discussed by Jeans: "The Mathematical Theory of Electricity and Magnetism," ed. 4, Cambridge University Press, 1923, p. 70.

animals with those obtained by similar leads in man might throw considerable light upon the interpretation of the human electrocardiogram.

#### EXPERIMENTAL OBSERVATIONS

*General Methods.*—In the experiments to be described we employed dogs of large size. They were fully anesthetized with sodium amytal given intravenously.\* The heart was exposed by splitting the sternum and opening the pericardial sac. The electrodes employed for standard indirect leads were small copper disks sewed under the skin; for direct and semidirect leads we used glass tubes of 3 or 4 mm. bore stoppered at one end with salted kaolin or gelatin and filled with copper sulphate solution into which a bright copper wire was thrust. The actual contact with the heart in direct leads was made by fat-free wool partially imbedded in the kaolin or gelatin plug and moistened with normal salt or Ringer's solution. To hold this in place and to protect the surface of the heart from injury a small piece of soft rubber tubing was slipped over the end of the glass tube.†

Two Einthoven galvanometers coupled together in tandem enabled us to take a direct or semidirect lead and a standard indirect lead simultaneously. In taking the former the exploring electrode was attached to the right-hand terminal of the galvanometer; the indifferent electrode was placed on the left hind leg. The arrangement was therefore such that relative negativity of the exploring electrode produced an upward deflection in the completed curve. Lead I was used as the standard lead; in recording this the galvanometer was employed at the normal sensitivity; a deflection of 1 cm. per millivolt. For the direct or semidirect leads the sensitivity of the galvanometer varied in different instances from one-fourth to one-twentieth of the normal.

To produce bundle-branch block we employed the method used by Lewis,<sup>5</sup> and by Wilson and Herrmann;<sup>6</sup> a small knife blade was thrust through the ventricular wall and the bundle branch cut or injured by pressure with the back of the blade. The location of the cut or injury was determined at the end of the experiment.

For measuring the time intervals of our curves we have employed the record measuring machine devised by Captain B. H. Elliott and manufactured by the Cambridge Instrument Company.

*A Typical Experiment.*—We may describe as typical of our usual method of procedure an experiment performed on January 24, 1930. The dog was a large bull terrier. Fig. 1 (Curve 621) shows Leads I and III taken simultaneously before the chest was opened. The heart was fully exposed in the usual way and then covered completely with

\*In our experiments this drug produced almost complete vagal paralysis.

†Such electrodes are not, as is often supposed, strictly nonpolarizable. If two of them are placed in contact with copper sulphate solution and connected with the terminals of the string galvanometer, an e.m.f. of ten millivolts suddenly introduced into the circuit will cause evident overshooting due to polarization capacity. This effect is less pronounced the greater the area of the surface of contact between metal and solution.

a large pad of gauze, about 1.5 cm. in thickness, soaked in warm normal salt solution. A series of curves was then taken by leading from various points on this pad to the left leg. (Fig. 2, left hand column.) Through an error in attaching the lead wires these curves were taken in such a way that relative negativity of the leg electrode rather than the exploring electrode yielded an upward deflection. In taking the first curve the exploring electrode was placed in contact with that part of the pad which rested upon the right basal margin of the heart. With each succeeding curve it was moved downward and to the left toward the cardiac apex a distance of approximately 2 cm. The final curve was taken from that part of the pad which lay upon the apex of the left ventricle. The galvanometer was employed at one-fifth the normal sensitivity; that is

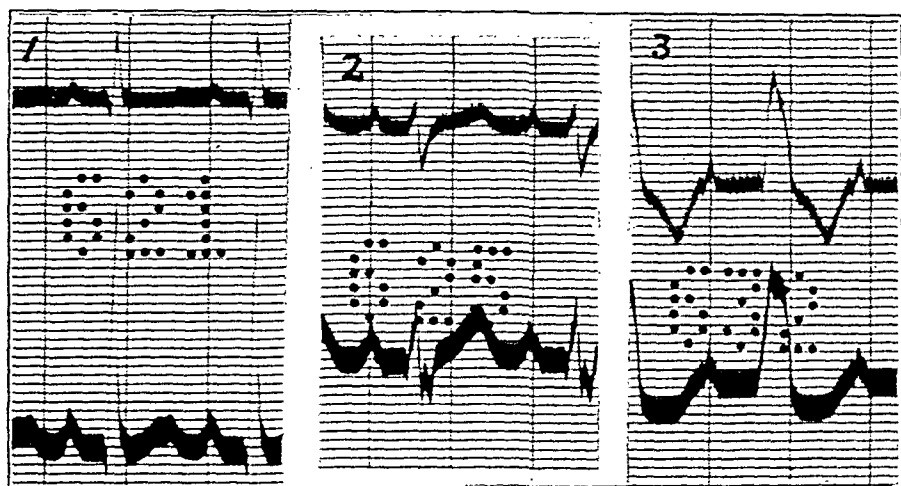


Fig. 1.—Experiment of Jan. 24, 1930. No. 621: Leads I and III before opening the dog's chest. No. 625: Leads I and III after pressure upon the right branch of the His bundle. No. 632: Leads I and III after section of the left branch of the His bundle.

to say, the tension of the string was so adjusted that 10 millivolts produced a deflection of 2 cm.

After this series of curves was obtained, the pad was removed and two attempts were made to produce right branch block by pressing upon the right branch of the His bundle with the back of a small knife blade thrust through the wall of the conus just below the pulmonary valve. The second attempt was apparently successful; the resulting change in the form of the electrocardiogram in Leads I and III is shown in Fig. 1 (Curve 625). The heart was again covered with the gauze pad and an-

Fig. 2.—Experiment of Jan. 24, 1930. Each column shows a series of five semidirect leads taken through a pad of gauze placed upon the exposed heart and recorded simultaneously with Lead I. Left-hand column: Taken while the cardiac mechanism was normal. The semidirect leads are upside down (see text). The sensitivity of the galvanometer was normal for Lead I and one-fifth normal for the semidirect leads. Middle column: Right branch block is present. The sensitivity of the galvanometer was one-fourth normal for the semidirect leads. Right-hand column: Left branch block is present. The sensitivity of the galvanometer was one-fifth normal for the first three and one-twentieth normal for the last two semidirect leads. The number on each curve gives the interval in seconds by which the chief upstroke of the semidirect lead follows the onset of R in Lead I. The time marks on the curves indicate intervals of 0.2 second.

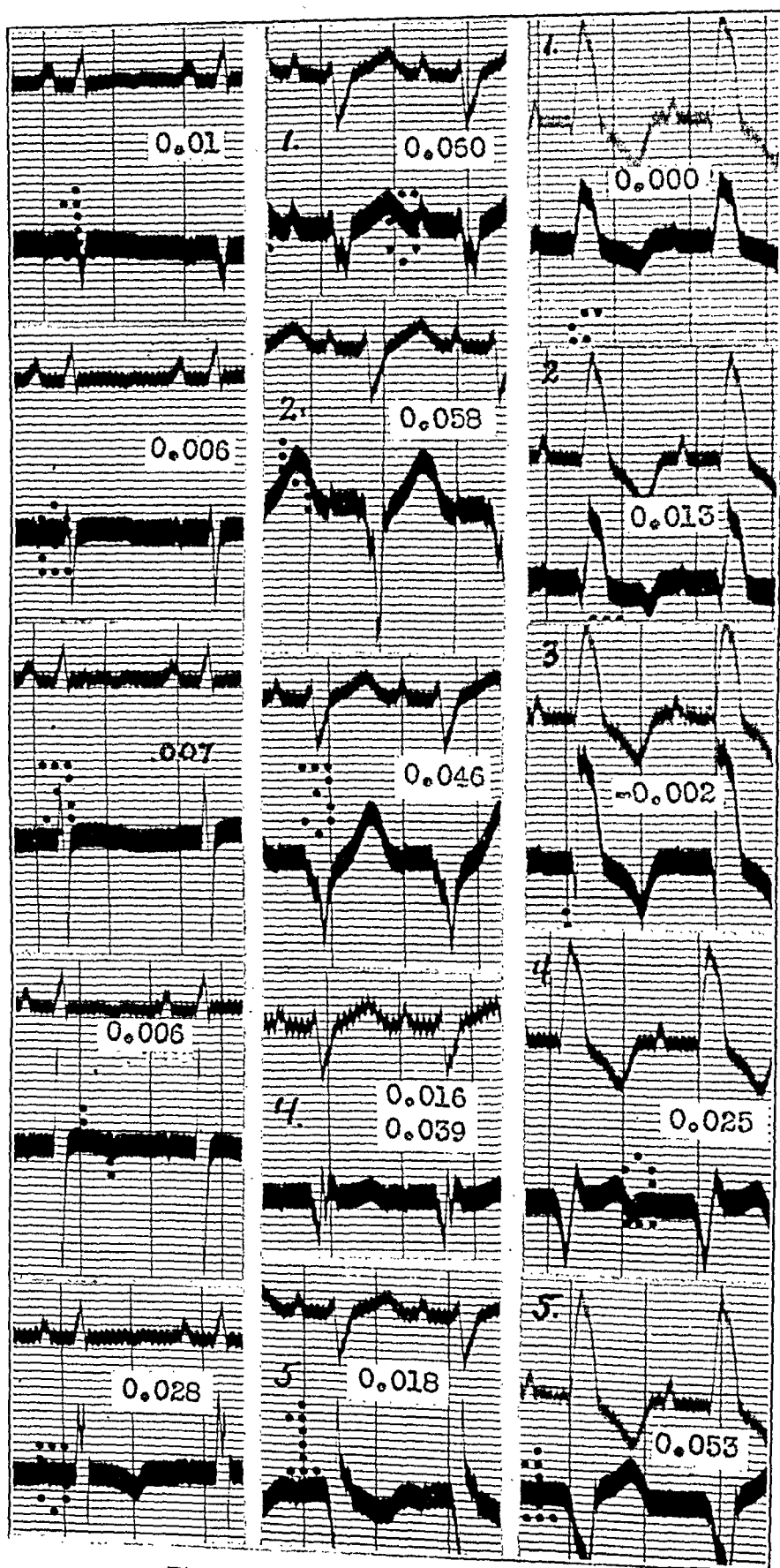


Fig. 2. (See legend on opposite page.)

other series of semidirect leads was taken in the same manner as before, except that the lead wires were now properly connected so that relative negativity of the exploring electrode produced an upward deflection. These curves are shown in Fig. 2 (middle column). Of the five curves taken only the last was from that part of the pad overlying the left ventricle. The part of the pad from which the first curve was taken lay beyond the atrioventricular groove. The galvanometer was used at one-fourth the normal sensitivity.

Shortly after these curves were taken the right branch of the His bundle began to recover and within a few minutes the electrocardiogram had returned to the normal type. Two attempts were then made to cut the left branch; the second was apparently successful; the form of the resulting electrocardiogram in Leads I and III is shown in Fig. 1 (Curve 632). The gauze pad was then reapplied and a third series of semidirect leads was taken as before. The first three curves were taken with the galvanometer at one-fifth the normal sensitivity; in taking the last two curves, however, the sensitivity was reduced to one-twentieth normal in order to keep the large downward deflections of the semidirect and the upward deflections of the standard lead both on the narrow film.

A short time after these curves were taken complete heart-block developed; the heart gradually dilated and the animal died. Examination of the right side of the ventricular septum showed two large subendocardial hemorrhages, one on either side of the main stem of the right bundle branch about one centimeter above the base of the anterior papillary muscle. Examination of the left side of the septum showed a deep gash which obviously severed the main stem of the left bundle branch completely. It lay just beneath the aortic valve and one of the valve cusps had been cut at its base. The resulting high-grade aortic insufficiency was probably partly responsible for the final dilatation of the heart.

*Additional Observations.*—In Fig. 3 we show some curves taken during an experiment performed on January 17, 1930. Curve 602 shows Leads I and III taken after section of the left bundle-branch just below the aortic valves. Curve 603 shows Lead I and a direct lead from the right central region; Curve 604 shows Lead I and a direct lead from the left apex. After these curves were made the heart was covered with a pad of gauze soaked in warm normal salt solution and a series of five semidirect leads was taken as in the experiment previously described. The curves shown in Fig. 3 (Curves 605-1-3-5) are the first, third, and fifth of this series. The sensitivity of the galvanometer was unfortunately not recorded; it was probably one-tenth or one-twentieth normal for the direct leads and one-fourth or one-fifth normal for the semidirect leads. The indifferent electrode was placed on the left hind leg.

*Description of Experimental Curves.*—With regard to the form and amplitude of the curves which they obtained by leading directly from the ventricular muscle to the chest wall, Lewis and Rothschild<sup>3</sup> make

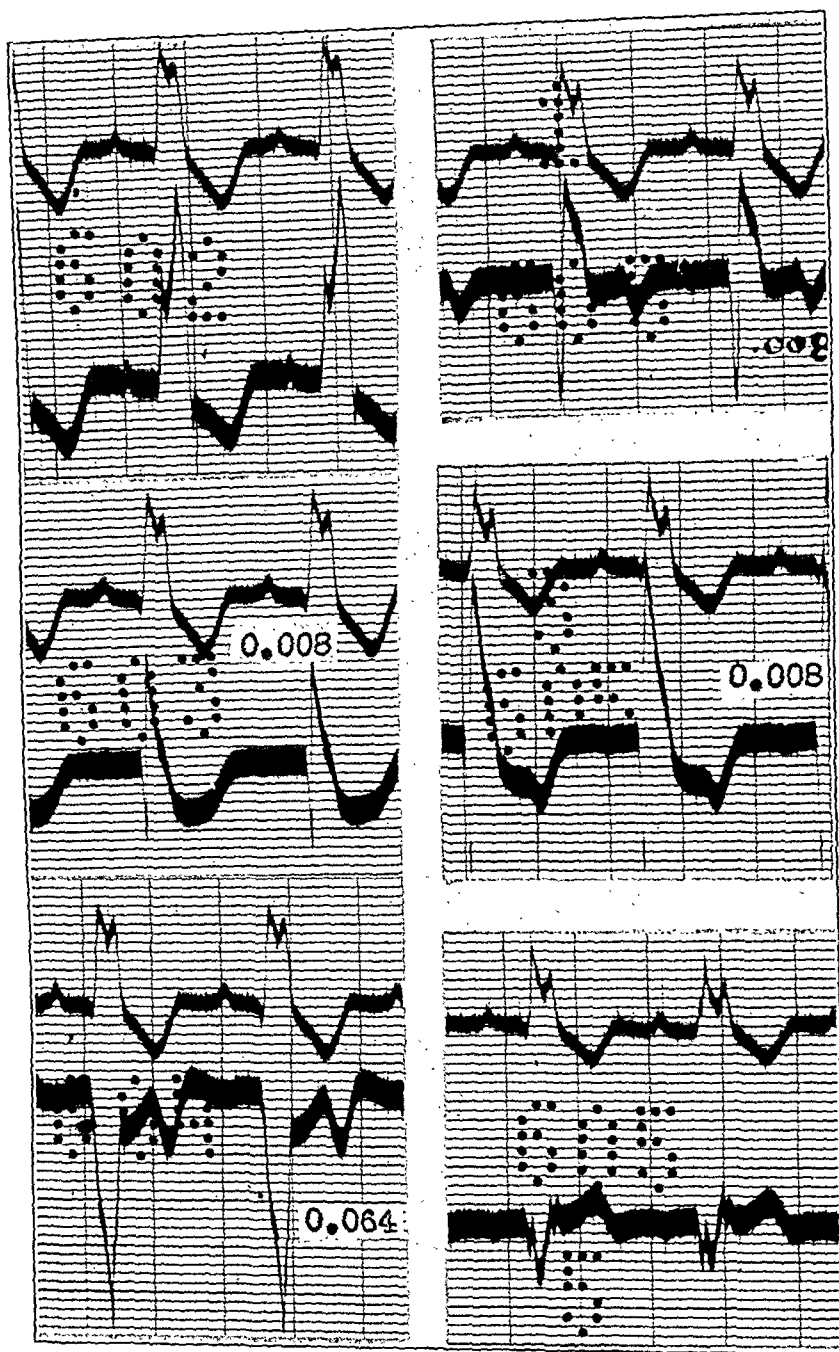


Fig. 3.—Experiment of Jan. 17, 1930. No. 602: Leads I and III after section of the left branch of the His bundle. No. 603: Lead I and a direct lead from the right central region. No. 604: Lead I and a direct lead from the left apex. No. 605: 1, 3, 5: The first, third and fifth of a series of five semidirect leads taken through a pad of gauze placed upon the heart.

the following statement: "The form of the curves taken directly from the ventricle by a single contact is variable. The majority of such curves show an initial dip of variable extent (2-35 millivolts). This dip is relatively slow and usually unbroken, but it may be notched; it



represents the first or extrinsic deflection. There may be a return to the base line before the intrinsic deflection is recorded, but more commonly, the onset of the intrinsic deflection terminates the dip. The upstroke is always very abrupt, and the recorded image of the fiber is consequently faint. Its amplitude, measured from its point of origin, is always considerable (10-80 millivolts)."

The curves obtained by semidirect leads may be described in very similar terms. These curves also show an initial dip of variable extent (1-20 millivolts), which is relatively slow and may be unbroken or notched. It is sometimes preceded by a small upright deflection and this is also true of the corresponding deflection of direct leads. This initial dip is followed by an abrupt upward movement of considerable amplitude (5-20 millivolts), which is ordinarily the steepest deflection of the ventricular complex. When this chief upstroke occurs early, it usually carries the string far above the base line; in such cases the initial downward movement is ordinarily of small amplitude, but there are occasional exceptions to this rule. When the chief upstroke occurs late, it usually carries the string only to the base line or a little way beyond it; in such cases the initial downward movement is of large amplitude. Although the upstroke under consideration is generally by far the sharpest deflection of the ventricular complex, being depicted by the thinnest line because it is written by the most rapid movement of the string, it is sometimes little, if at all, steeper than the other deflections. In some instances no deflection of this character is present.

The chief difference between the curves obtained by direct leads and those obtained by semidirect leads lies in the voltages which are on the average much greater in the former. There is also a difference in the relative steepness of the chief upstroke which is greater in direct leads, permitting the more certain identification of this deflection.

We may now examine the curves illustrated in Figs. 2 and 3 in greater detail. In the case of the undamaged heart (Fig. 2, first column), the curves from that part of the gauze pad which lay upon the right ventricle (2, 3, and 4) show a chief upstroke (actually a downstroke because of the error in connecting the lead wires previously mentioned) which comes early, about 0.007 second after the onset of R in Lead I. In the single curve (5), taken from that part of the pad which lay upon the left apex, this deflection comes a little later; about 0.028 second after R. In the first curve, which was taken from that part of the pad which lay above the atrioventricular groove, the ventricular deflections are small.

When right branch block was present, the chief upstroke of those curves which were taken from that part of the pad which lay upon the right ventricle (2, 3, and 4) begins late; about 0.05 or 0.06 second after the onset of R in Lead I. The single curve taken from that part of the

pad which lay upon the left apex (5), on the other hand, shows an early chief upstroke, which begins about 0.018 second after the onset of R. In the fourth curve of this series the chief upstroke is early (0.016 after R), but of small amplitude; a second smaller and more gradual upstroke occurs late (0.39 second after R). It may be pointed out here that curves of transitional type were frequently obtained from that part of the pad which lay near the interventricular groove; in such curves there were sometimes two prominent upstrokes, one early, the other late; in other instances there was no chief upstroke at all; and in still others the chief upstroke fell in a position intermediate between its position in the curves taken more toward the right base and that which it occupied in those taken more toward the left apex. It will be noted that the chief upstrokes of the first three curves of this series do not rise above the base line; the ventricular complexes resemble in general form the ventricular complexes of Lead I.

Turning now to the left branch block series, we find that in those curves (1, 2, and 3) obtained by leading from portions of the pad that lay upon the right ventricle the chief upstroke is early (practically synchronous with R of Lead I) and carries the fiber far above the base line where it remains throughout the remainder of the QRS interval. These complexes resemble in general form the ventricular complexes of Lead I. In the last curve of the series (5), which was taken from that part of the pad which lay upon the left apex, the chief upstroke is late (0.053 second after R) and rises only a little way above the base line, so that the ventricular complex is of the opposite type. The fourth curve is of the transitional type; the chief upstroke occurs about 0.025 second after R.

The curves shown in Fig. 3, which were obtained from a second animal with left branch block, may be compared with those just described. The complexes obtained by leading directly from the right central region (Curve 603) and those obtained by semidirect leads from that part of the pad which lay upon the right ventricle (Curves 605-1-3) are very similar in form. The chief upstroke occurs at approximately the same time in both. The resemblance between the complexes obtained by leading directly from the left ventricle and those obtained from that part of the pad which lay upon it is less striking. The latter complexes are of the transitional type.

*Comments.*—The experiments described show without question that when bundle-branch block is present the chief upstroke of the ventricular complex in semidirect leads is early when the exploring electrode is placed close to the ventral surface of the contralateral ventricle and late when this electrode is placed close to the surface of the homolateral ventricle. In the former case the fiber usually remains above, in the latter case it usually remains below the base line throughout the greater

With reference to the intrinsic deflection in direct leads from the ventricle, in which only one electrode (the exploring electrode) was placed upon the muscle, the other (the indifferent electrode) being in contact with the chest wall, it was shown that the time of this deflection, with reference to the deflections of Lead II, was not altered by moving the indifferent electrode. It was also demonstrated that the intrinsic deflection fell later and later as the exploring electrode was moved up the conus arteriosus, and that it disappeared when the muscle boundary at the junction of conus and pulmonary artery was crossed.

We have repeated these last experiments. In leads from the conus arteriosus the ventricular complex ordinarily begins with a small upward deflection followed by a sharp and deep dip. This dip is terminated by the onset of the intrinsic deflection which carries the string back to the base line or a little way beyond it. The intrinsic deflection is late. When the exploring electrode is moved across the muscle border on to the pulmonary artery, the form of the ventricular complex changes and the chief upstroke is early. This procedure is not equivalent to moving the exploring electrode away from the heart along a line normal to its surface, for it involves placing this electrode opposite an opening, the valve orifice, in the ventricular wall. We have pointed out elsewhere<sup>8</sup> that the potential of any point in the body, in so far as it is influenced by the heart beat, is determined theoretically according to the following equation:

$$V = \Phi \Omega$$

where  $V$  is the potential of the point;  $\Phi$ , a constant; and  $\Omega$ , the solid angle subtended at this point by the surface which separates active from resting muscle. This angle is positive or negative according as the positive or the negative side (resting or active side) of the surface in question faces toward the apex of the cone which defines it. Throughout the greater part of the QRS interval a point on the pulmonary artery near the valve and one on the conus arteriosus must lie on opposite sides of this surface and must have potentials unlike in sign. The former facing toward the interior of the heart is on the negative side; it becomes negative early and remains so until the greater part of the ventricular muscle has passed into the active state. The latter remains negative only until the activation of the subendocardial muscle of the conus places it on the positive side of the active-resting surface.

Lewis and Rothschild<sup>3</sup> mention that when the exploring electrode is introduced into the ventricular cavity an early reading (i.e., an early intrinsic deflection) is obtained even when the electrode is not in contact with the endocardial surface of the heart except through the blood. This observation, which we have also made, indicates that intrinsic or intrinsic-like deflections are, in the case of the ventricular muscle, by no means peculiar to direct leads.

In the case of the auricular muscle semidirect leads yield no sharp deflections. We have pointed out that when, starting with a direct lead, we move the exploring electrode away from the heart wall through a conducting medium, we tend to decrease the influence of the muscle units with which it was originally in contact and to increase relatively the influence of the muscle units that surround them. The effect must be somewhat, although not exactly, the same as that produced by increasing the size of the electrode. It is clear that the potential of the electrode at any instant must be determined by the mean potential of the area with which it is in contact. If the potential of some points of this area is changing in one direction and the potential of other points is changing in the opposite direction the potential of the exploring electrode may remain nearly stationary. In the case of the auricle, increasing the size of the exploring electrode causes a rapid degradation of the recorded curve with a disappearance of all sharp deflections, because such neighboring points as are arranged radially with reference to the sinus node pass through similar changes in potential, not simultaneously but in succession, displaying similar potentials when they bear a similar relation to the crest of the excitation wave. No similar effect occurs in the case of the ventricle. Here the excitatory process spreads outward through the ventricular wall and all points over relatively large areas pass through similar potential levels at the same time. At any instant the average potential over a small area and the average potential over a large area are therefore very nearly equal.

#### CLINICAL OBSERVATIONS

For precordial leads we employed small copper disks, about one inch in diameter, which were soldered to binding posts. The skin was cleaned with alcohol and with soap and water. The electrodes were smeared with a commercial preparation manufactured for use in diathermy treatments and were held in place with adhesive tape. Four or five electrodes were arranged diagonally across the precordium, the first being placed, as a rule, to the right of the sternum in the third or fourth intercostal space near the right border of cardiac dullness, and the last beyond the left border of dullness in the region of the apex beat. The indifferent electrode was placed on the left leg. The galvanometer was employed at approximately one-half the normal sensitivity and Lead I was recorded simultaneously with each precordial lead.

The exploring electrode was, of course, considerably further from the surface of the heart in these leads than in the semidirect leads employed in our animal experiments. In order not to increase the distance to an extent that would make comparison hazardous, we chose, in so far as possible, patients of slight build, avoiding the obese and the emphysematous. It should be noted that the left ventricle is much less favor-

ably situated for our purpose than the right. The surface which it presents anteriorly is small in extent and is covered by a relatively thick layer of tissue. Leads from the central precordium, which overlies the anterior surface of the right ventricle, are therefore of more value for comparison with the experimental leads than those from the region of the apex beat or beyond. It is naturally not possible to say precisely where the interventricular groove lies with reference to the landmarks of the anterior chest wall in any given case, since this must depend upon

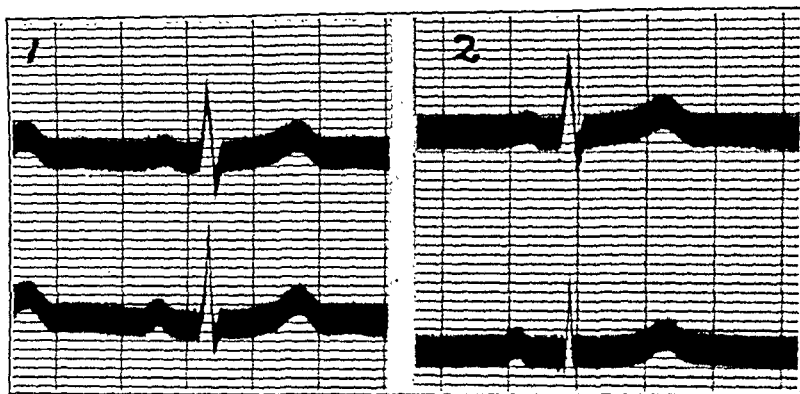


Fig. 4.—Case 1. Leads I and II on the left; Leads I and III on the right. The electrocardiogram is of the normal type.

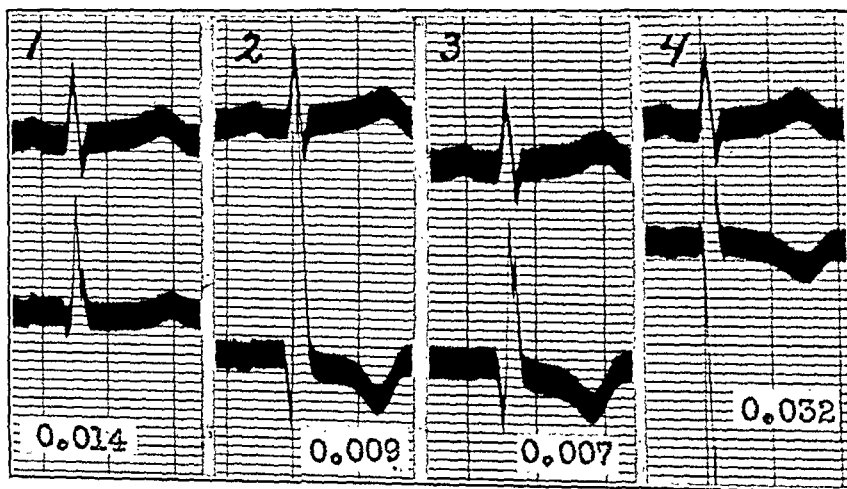


Fig. 5.—Case 1. A series of four precordial leads, each recorded simultaneously with Lead I. The introduction of one millivolt into the circuit produced a deflection of 7 mm. in semidirect Leads I and III, and of 8 mm. in semidirect Leads II and IV.

the position of the heart and the relative size of the two ventricles. By arranging a number of electrodes along a line approximately at right angles to this groove, this difficulty is to a large extent avoided. It is possible, however, that in some instances our line of electrodes was not extended sufficiently far to the left to obtain semidirect leads from the left ventricular surface.

CASE 1.—The patient was a boy, aged seventeen years, who gave a history of rheumatic fever and chorea. On examination there was questionable slight enlargement of the heart and a soft systolic murmur at the apex and at the base.

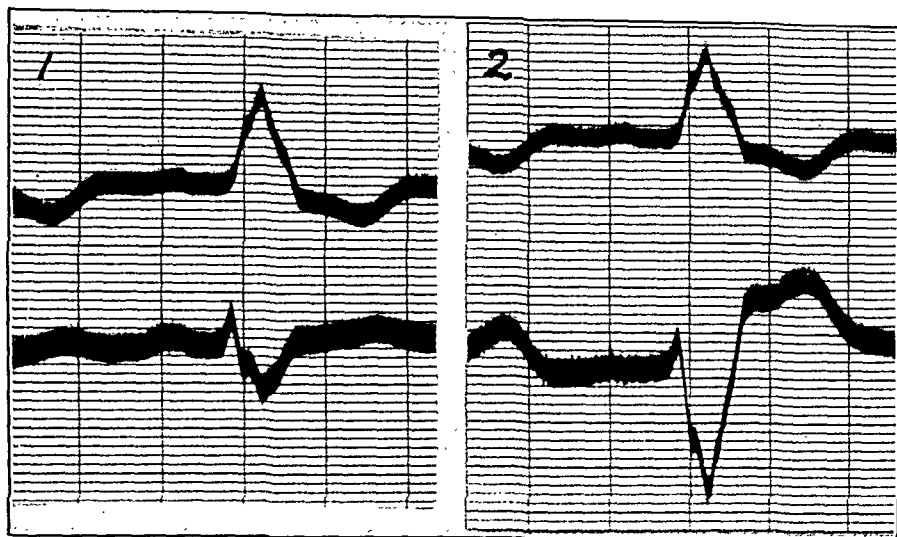


Fig. 6.—Case 2. Leads I and II are shown on the right, and Leads I and III on the left. Typical bundle-branch block of the common type with a QRS interval of 0.169 second.

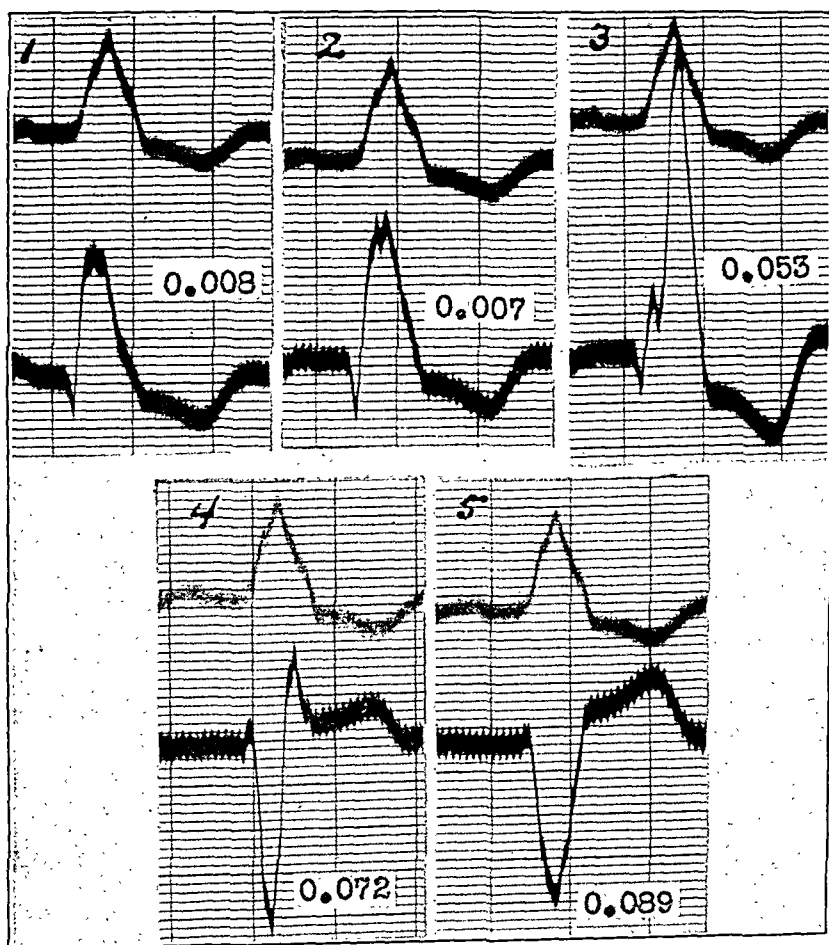


Fig. 7.—Case 2. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 7 mm. in Lead I, 5 mm. in Lead II, 8.5 mm. in Lead III, 6 mm. in Lead IV, and 5 mm. in Lead V.

There was a third sound in early diastole at the apex. Slight rheumatic involvement of the mitral valve was suspected. The electrocardiogram was of the normal type (Fig. 4). Four precordial leads were taken: (1) from the right sternal edge at the fourth costal cartilage; (2) from the left sternal edge at the fourth costal cartilage; (3) from a point midway between (2) and (4); (4) from the fifth intercostal space just beyond the nipple line. The curves are shown in Fig. 5; in the first three the onset of the chief upstroke is relatively early (0.007 to 0.014 second after the onset of R in Lead I) and the preliminary downward movement of the fiber is of small amplitude. In the fourth curve the downward movement is large and the upstroke is later (0.032 second after R). These curves may be compared with those shown in the left-hand column of Fig. 2.

CASE 2.—The patient was a man, aged sixty-one years, with a history of long standing hypertension (systolic blood pressure—225 mm. Hg) and cardiac weakness with shortness of breath, engorgement of the liver, and edema. The heart was greatly enlarged; there were no valve lesions. The electrocardiogram showed typical bundle-branch block of the common type (Fig. 6) with a QRS interval of approximately 0.169 second. A series of five precordial leads was taken: (1) from the right sternal edge in the fourth intercostal space; (2) from the left sternal

TABLE I (CASE 2)

| TIME   | V <sub>F</sub> | -V <sub>1</sub> +V <sub>F</sub> | -V <sub>1</sub> | -V <sub>5</sub> +V <sub>F</sub> | -V <sub>5</sub> | I    | II    | II (CAL) | III   | α DE-<br>GREES |
|--------|----------------|---------------------------------|-----------------|---------------------------------|-----------------|------|-------|----------|-------|----------------|
| 0.0    | 0.0            | 0.0                             | 0.0             | 0.0                             | 0.0             | 0.0  | -2.9  | 0.0      | 0.0   | -              |
| 0.0062 | 1.0            | -2.0                            | -3.0            | 0.0                             | -1.0            | 0.0  | 0.0   | 1.5      | 1.5   | 90             |
| 0.0124 | 3.1            | -9.0                            | -12.1           | 0.0                             | -3.1            | 0.0  | 4.4   | 4.6      | 4.6   | 90             |
| 0.0186 | 5.6            | -19.0                           | -24.6           | 10.0                            | 4.4             | 1.5  | 10.2  | 9.2      | 7.7   | 81             |
| 0.0248 | 8.4            | -10.0                           | -18.4           | 11.7                            | 3.3             | 3.9  | 12.5  | 14.6     | 10.7  | 75             |
| 0.0310 | 3.3            | 12.0                            | 8.7             | -1.7                            | -5.0            | 6.9  | 8.1   | 8.4      | 1.5   | 39             |
| 0.0372 | 2.3            | 55.0                            | 52.7            | -17.0                           | -19.3           | 11.5 | 0.7   | 2.3      | -9.2  | -21            |
| 0.0434 | -11.1          | 75.0                            | 86.1            | -51.5                           | -40.4           | 19.2 | -7.3  | -7.0     | -26.2 | -45            |
| 0.0496 | -18.2          | 84.0                            | 102.2           | -86.6                           | -68.4           | 25.4 | -14.7 | -14.6    | -40.0 | -51            |
| 0.0558 | -21.3          | 87.0                            | 108.3           | -115.0                          | -93.7           | 30.0 | -16.2 | -17.0    | -47.0 | -51            |
| 0.0620 | -21.0          | 91.0                            | 112.0           | -137.0                          | -116.0          | 32.4 | -13.9 | -15.3    | -47.7 | -48            |
| 0.0682 | -22.1          | 103.0                           | 125.1           | -153.0                          | -130.9          | 33.8 | -14.7 | -16.2    | -50.0 | -48            |
| 0.0744 | -24.7          | 91.5                            | 116.2           | -176.0                          | -151.3          | 37.0 | -17.6 | -18.5    | -55.5 | -49            |
| 0.0806 | -27.5          | 92.0                            | 119.5           | -195.0                          | -167.5          | 42.5 | -21.3 | -20.0    | -62.5 | -48            |
| 0.0868 | -32.4          | 94.5                            | 126.9           | -198.0                          | -165.6          | 47.7 | -22.8 | -24.8    | -72.5 | -50            |
| 0.0940 | -36.8          | 91.0                            | 127.8           | -202.0                          | -165.2          | 51.6 | -29.4 | -29.4    | -81.0 | -51            |
| 0.1002 | -39.3          | 83.0                            | 122.3           | -218.0                          | -178.7          | 50.0 | -30.2 | -34.0    | -84.0 | -54            |
| 0.1064 | -36.4          | 72.0                            | 108.4           | -198.0                          | -161.6          | 44.7 | -28.6 | -32.3    | -77.0 | -55            |
| 0.1126 | -33.8          | 55.0                            | 88.8            | -183.0                          | -149.2          | 40.0 | -26.5 | -30.7    | -70.7 | -56            |
| 0.1188 | -31.2          | 45.0                            | 76.2            | -170.0                          | -138.8          | 35.4 | -24.3 | -29.6    | -64.0 | -58            |
| 0.1250 | -26.5          | 34.0                            | 60.5            | -137.0                          | -110.5          | 31.6 | -22.0 | -23.9    | -55.5 | -56            |
| 0.1312 | -24.6          | 26.0                            | 50.6            | -113.0                          | -88.4           | 26.2 | -20.6 | -23.8    | -50.0 | -58            |
| 0.1374 | -21.5          | 21.0                            | 42.5            | -85.0                           | -63.5           | 21.6 | -18.4 | -21.4    | -43.0 | -60            |
| 0.1436 | -18.4          | 16.0                            | 34.4            | -63.2                           | -44.8           | 20.0 | -15.4 | -17.6    | -37.6 | -58            |
| 0.1498 | -13.6          | 11.0                            | 24.6            | -48.2                           | -34.6           | 17.7 | -12.5 | -11.5    | -29.2 | -53            |
| 0.1560 | -10.9          | 6.0                             | 16.9            | -25.0                           | -14.1           | 15.4 | -10.3 | -8.2     | -24.6 | -49            |
| 0.1620 | -9.5           | 1.0                             | 10.5            | -6.7                            | 2.8             | 13.1 | -7.3  | -7.7     | -20.8 | -51            |
| 0.1682 | -5.9           | -4.0                            | 1.9             | 16.7                            | 22.6            | 8.5  | -6.6  | -4.6     | -13.1 | -50            |
| 0.1744 | -1.7           | -9.0                            | -7.3            | 40.0                            | 41.7            | 2.3  | -2.9  | -1.5     | -3.8  | -53            |
| 0.1806 | -0.2           | -15.0                           | -14.8           | 43.0                            | 43.2            | -2.3 | -0.7  | -1.5     | 0.8   | -170           |
| 0.1868 | 3.8            | -18.0                           | -21.8           | 45.0                            | 41.2            | -5.4 | 0.0   | 3.1      | 8.5   | 129            |

The measurements are expressed in units of 0.02 millivolt. V<sub>F</sub> is the potential of the left leg. -V<sub>1</sub>+V<sub>F</sub> is precordial Lead I as recorded. -V<sub>1</sub> is minus the potential of precordial point 1. -V<sub>5</sub>+V<sub>F</sub> is precordial Lead V as recorded. -V<sub>5</sub> is minus the potential of precordial point 5. II (cal) is Lead II calculated by the addition of Leads I and III.

edge in the fifth intercostal space; (3) from the sixth rib in the midclavicular line; (4) from the sixth intercostal space 2.5 cm. medial to the anterior axillary line, and (5) from the seventh rib in the anterior axillary line. These curves are shown in Fig. 7; in the first two the chief upstroke is early (about 0.007-0.008 second after the onset of R in Lead I) and the complexes resemble those of Lead I in form. In the third curve the main upstroke is deeply notched; the chief upward movement occurs about 0.053 second after R. In the last two curves the chief upstroke is late (0.072 to 0.089 second after R) and rises only a little way above the base line.

In order to show that potential variations of the indifferent electrode were not an important factor in determining the form of the ventricular complexes of these precordial leads we have computed the potential variations of the first and fifth points investigated. The numerical data are given in Table I. The original curves were enlarged about five diameters by optical projection, traced on coordinate paper, and measured. All measurements are expressed in units of 0.02 millivolt. We give the potential values corresponding to instants separated by equal time intervals. The table gives in order the potential of the left leg ( $V_F$ ); the recorded and corrected potentials of Points 1 and 5; and the measurements of the ventricular complexes of the standard leads. In the case of Lead II we give both the measurements of the recorded curve and the values calculated by adding the deflections of Leads I and III. In the last column of the table the angle  $\alpha$  which defines the position of the electrical axis is given. It will be noted that during the early part of the QRS interval there is a counter-clockwise rotation of the electrical axis of the type described by Lewis<sup>5</sup> in cases of branch block of the common type. While the potential variations of the indifferent electrode are by no means without influence upon the form of the precordial curves, the elimination of this influence does not materially alter the general outline of the ventricular complex or the time of occurrence of the chief upstroke.

TABLE II

| CASE 3 |       |            |        |            |        | CASE 7 |       |
|--------|-------|------------|--------|------------|--------|--------|-------|
| TIME   | $V_F$ | $-V_3+V_F$ | $-V_3$ | $-V_4+V_F$ | $-V_4$ | TIME   | $V_F$ |
| 0.0    | 0.0   | 0.0        | 0.0    | 0.0        | 0.0    | 0.0    | 0.0   |
| 0.008  | 0.6   | -10.0      | -10.6  | -4.0       | -4.6   | 0.0098 | -0.6  |
| 0.016  | 4.0   | -34.0      | -38.0  | -16.0      | -20.0  | 0.0196 | -0.6  |
| 0.024  | 4.6   | -56.0      | -60.6  | -34.0      | -38.6  | 0.0294 | 2.3   |
| 0.032  | 3.3   | -70.0      | -73.3  | -50.0      | -53.3  | 0.0392 | 16.0  |
| 0.040  | -4.0  | -84.0      | -80.0  | -66.0      | -62.0  | 0.0490 | 54.0  |
| 0.048  | -18.3 | -94.0      | -75.7  | -80.0      | -61.7  | 0.0588 | 78.0  |
| 0.056  | -29.6 | -76.0      | -46.4  | -82.0      | -52.4  | 0.0686 | 85.0  |
| 0.064  | -28.0 | -10.0      | 18.0   | -82.0      | -54.0  | 0.0784 | 62.0  |
| 0.072  | -29.0 | 16.0       | 45.0   | -84.0      | -55.0  | 0.0882 | 33.3  |
| 0.080  | -34.0 | 40.0       | 74.0   | -86.0      | -52.0  | 0.0980 | 5.3   |
| 0.088  | -41.3 | 30.0       | 71.3   | -90.0      | -48.7  | 0.1078 | -5.0  |
| 0.096  | -53.3 | -26.0      | 27.3   | -78.0      | -24.7  | 0.1176 | -15.0 |
| 0.104  | -51.0 | -40.0      | 11.0   | -50.0      | 1.0    | 0.1274 | -12.6 |
| 0.112  | -39.0 | -16.0      | 23.0   | -26.0      | 13.0   |        |       |
| 0.120  | -29.6 | 0.0        | 29.6   | 0.0        | 29.6   |        |       |
| 0.128  | -9.0  | 2.0        | 11.0   | 10.0       | 19.0   |        |       |
| 0.136  | -0.6  | 4.0        | 4.6    | 16.0       | 16.6   |        |       |
| 0.144  | 0.6   | 4.0        | 3.4    | 18.0       | 17.4   |        |       |

All measurements are given in units of 0.02 millivolt.

$V_F$  is the potential of the left leg.

$-V_3+V_F$  is the deflection in precordial Lead III as recorded;  $-V_4+V_F$  is the deflection in precordial Lead V as recorded.

$V_3$  is the potential of precordial point 3;  $V_4$ , the potential of precordial point 4.



CASE 3.—The subject was a woman, aged sixty-six years, who complained of palpitation, weakness, and dyspnea. Examination showed a large adenomatous goiter, and conspicuous enlargement of the heart. The blood pressure was moderately elevated (170/60); and there was considerable sclerosis of the peripheral arteries. A systolic and a diastolic murmur were heard in the aortic area and a systolic murmur and gallop rhythm at the apex. There were no signs of cardiac failure.

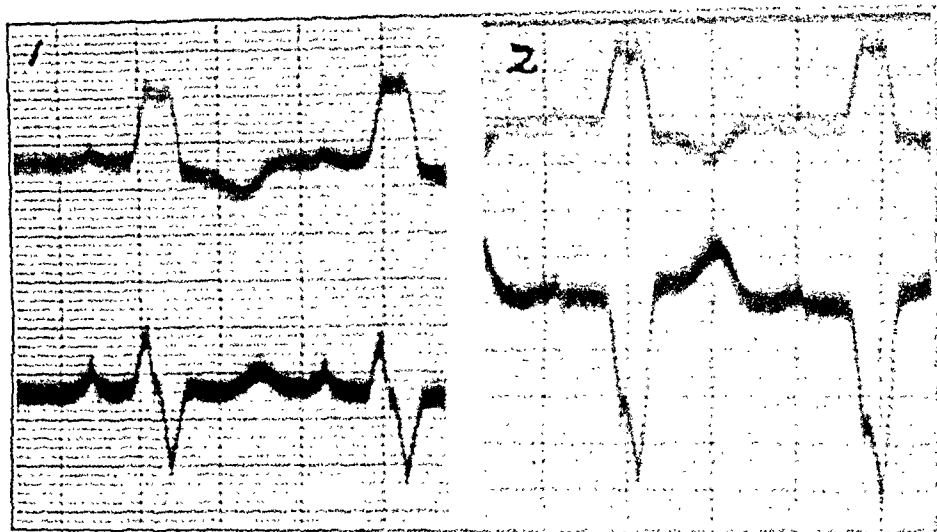


Fig. 8.—Case 3. Leads I and II on the left and Leads I and III on the right. Typical bundle-branch block of the common type. The QRS interval measures 0.124 second.

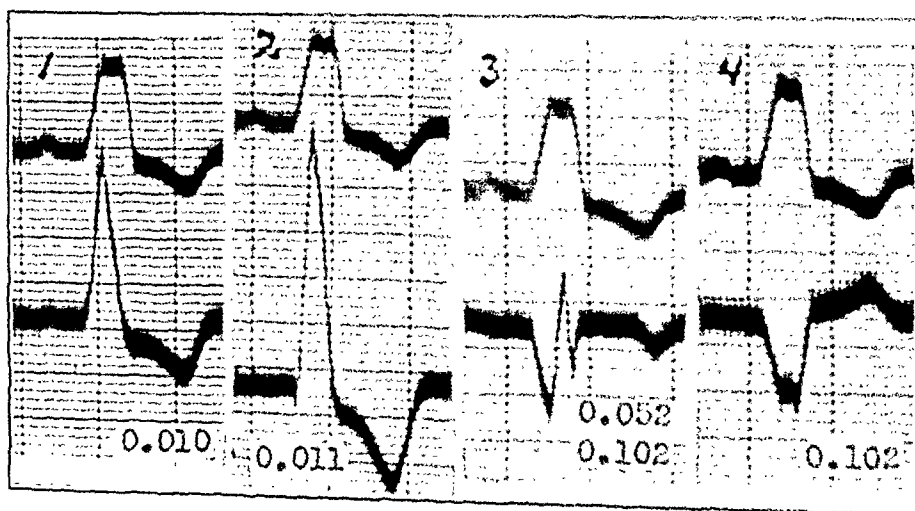


Fig. 9.—Case 3. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 5 mm. in Leads I, II, and IV, and of 4.5 mm. in Lead III.

The electrocardiogram showed typical branch block of the common type (Fig. 8) with a QRS interval of approximately 0.124 second. Four precordial leads were taken: (1) from the fourth intercostal space just to the right of the sternum; (2) from the fourth intercostal space just to the left of the sternum; (3) from the apex (fifth intercostal space, 11 cm. from the midline); (4) from the sixth intercostal space at the anterior axillary line (15 cm. from the midline). These curves are shown in Fig. 9. In the first two leads the chief ventricular upstroke is early (0.01 second after R); the third curve is of the transitional type with two up-

strokes; in the fourth curve the chief upstroke is very late (0.102 second after R) but not particularly sharp. In this case we have computed the potential variations of the third and fourth points investigated. The numerical data appear in Table II. While the recorded ventricular complexes are considerably altered by this cor-

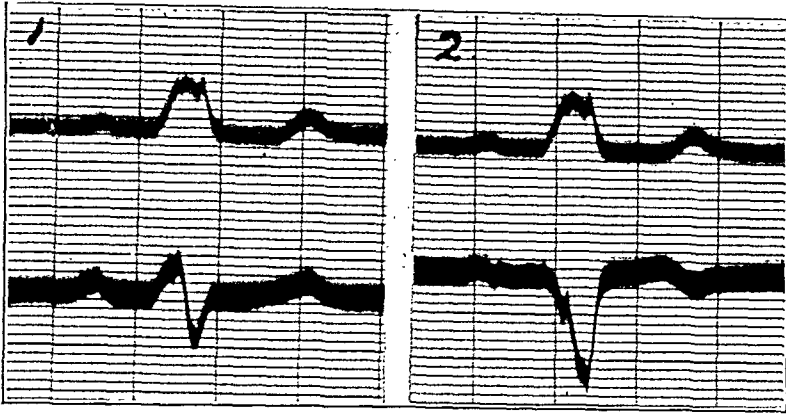


Fig. 10.—Case 4. Leads I and II on the left and Leads I and III on the right. Bundle-branch block of the common type with a QRS interval of 0.146 second.

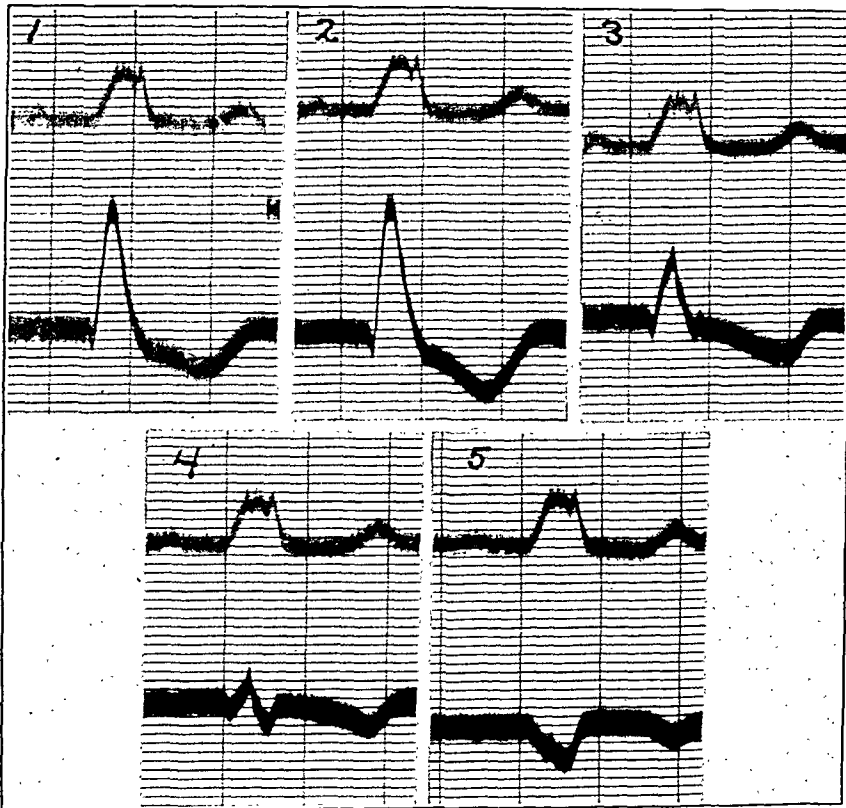


Fig. 11.—Case 4. A series of five precordial leads. In the semidirect leads one millivolt produced a deflection of 5.5 mm. in Lead I, 5 mm. in Leads II, III, IV, and V.

rection, their chief features remain. It is obvious that similar correction could not significantly change the form of the complexes of the first two leads.

CASE 4.—The subject was a man, aged sixty-seven years, with general arteriosclerosis. The heart was definitely enlarged; and there was a harsh systolic murmur both at the apex and at the base. The blood pressure was moderately raised

(150/80). There was evidence of mild cardiac weakness. The electrocardiogram showed typical branch block of the common type (Fig. 10) with a QRS interval of 0.146 second. Five precordial leads were taken: (1) from the fifth costal cartilage at the right sternal margin; (2) from the fifth costal cartilage at the left sternal margin; (3) from the fifth intercostal space 4 or 5 cm. from the left sternal margin; (4) from the apex (fifth intercostal space 2 cm. inside the anterior axillary line); (5) from the sixth intercostal space in the anterior axillary line. These curves are shown in Fig. 11; the chief upstroke is obviously early in the first two

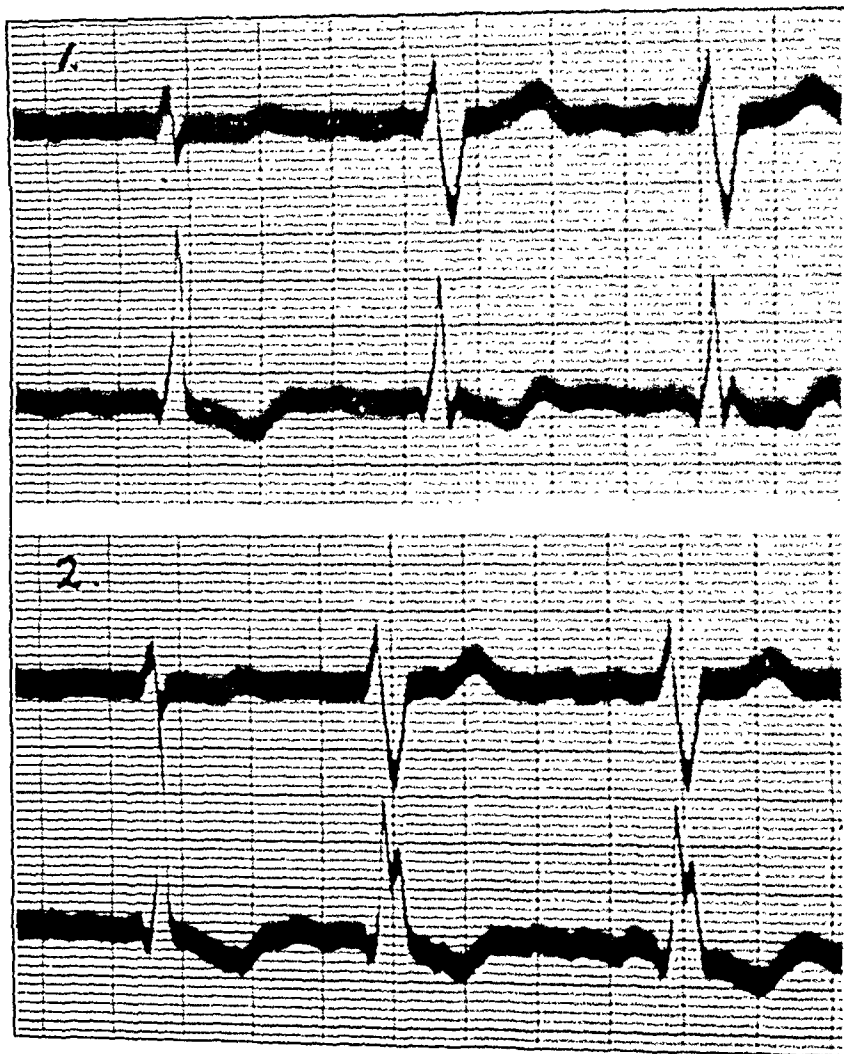


Fig. 12.—Case 5. Leads I and II above, and Leads I and III below. Auricular fibrillation is present. The first complex of each lead is of the normal type. The last two complexes are characteristic of branch block of the rare type. The QRS interval of the narrower complexes measures 0.099 second; that of the broader complexes, 0.135 second.

leads. In the remaining leads the curves are of small amplitude and show no sharp deflections; nevertheless, the principal upstroke is later.

CASE 5.—The patient was a boy, aged seventeen years, with typical mitral stenosis and auricular fibrillation. He gave a clear history of rheumatic fever. In the electrocardiogram two types of ventricular complexes occurred; during periods when the heart rate was slow the ventricular complexes were of the type suggesting slight right ventricular preponderance (QRS interval, 0.099 second); whenever the heart rate quickened there was a sudden transition to broad (QRS interval, 0.135 second) diphasic complexes of the type seen in the rare form of branch block

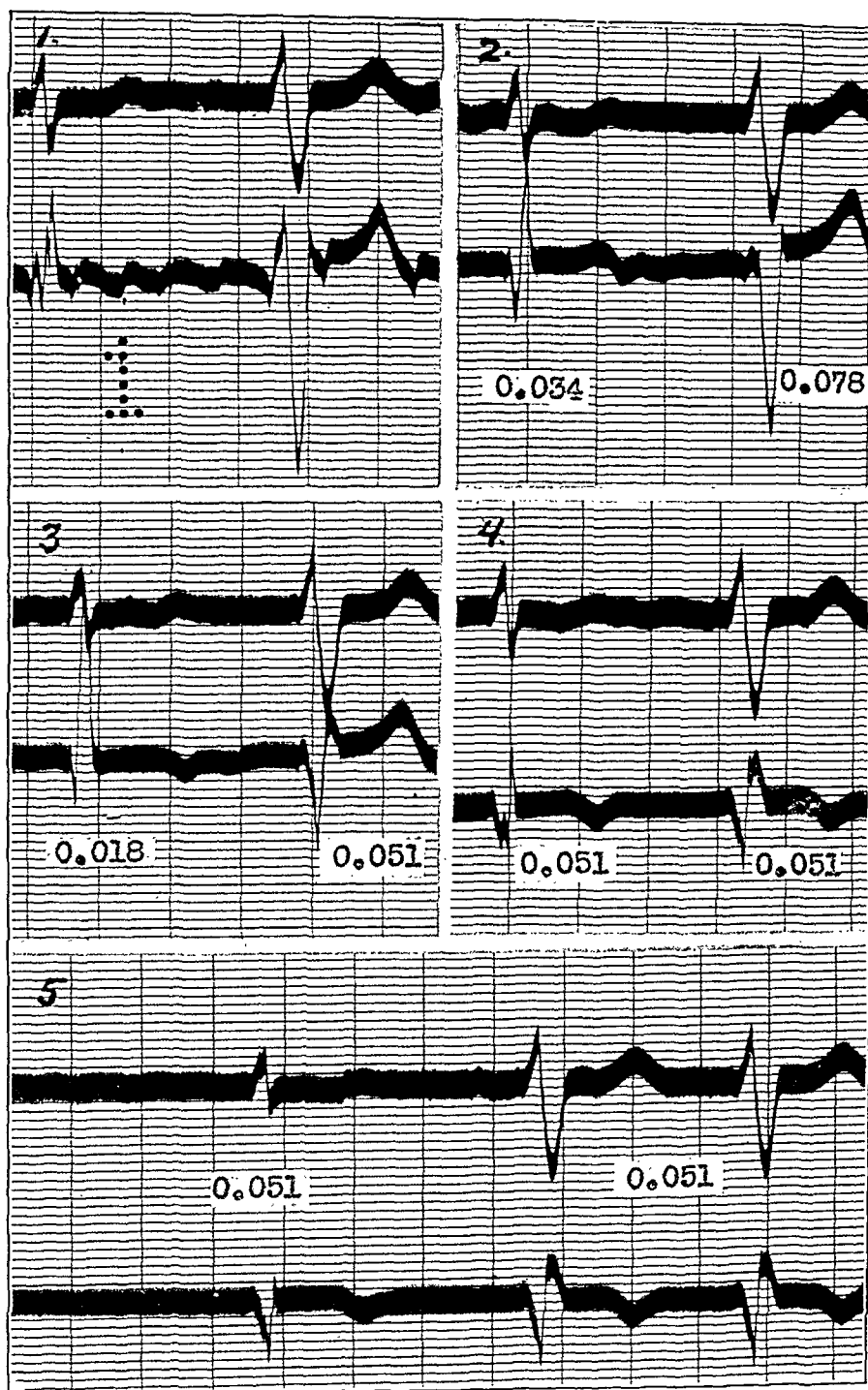


Fig. 13.—Case 5. A series of five precordial leads. The sensitivity of the galvanometer was approximately one-half normal for the first four semidirect leads and one-third normal for the fifth.

(Fig. 12). Five precordial leads were taken: (1) from the fourth intercostal space just to the right of the right border of cardiac dullness (5 cm. to the right of the right sternal margin); (2) from a point just to the left of the middle of the sternum at the level of the fifth costal cartilage; (3) from the fifth intercostal space just to the right of the left nipple line; (4) from the point of maximum pulsation; (5) from the seventh intercostal space in the anterior axillary line and just beyond the maximum impulse. These curves are shown in Fig. 13. In the first lead, which was taken over the right auricle, the auricular oscillations are very prominent. In the second and third leads the chief upstroke is relatively early when the ventricular complexes are of the normal type, and relatively late when they are of the abnormal type. In the last two leads the chief upstroke occurs at about the same time when the ventricular complexes are of the narrow type as when they are of the broad type; it is rather late in both cases. It should be noted that all of the complexes

TABLE III (CASE 5)

| TIME  | $V_F$<br>ABNORMAL<br>COMPLEXES | $-V_5+V_F$<br>ABNORMAL<br>COMPLEXES | $-V_5$<br>ABNORMAL<br>COMPLEXES | $V_F$<br>NORMAL<br>COMPLEXES | $-V_5+V_F$<br>NORMAL<br>COMPLEXES | $-V_5$<br>NORMAL<br>COMPLEXES |
|-------|--------------------------------|-------------------------------------|---------------------------------|------------------------------|-----------------------------------|-------------------------------|
| 0.0   | 0.0                            | 0.0                                 | 0.0                             | 0.0                          | 0.0                               | 0.0                           |
| 0.009 | -3.0                           | 6.0                                 | 9.0                             | 0.3                          | 3.0                               | 2.7                           |
| 0.018 | -2.0                           | 7.5                                 | 9.5                             | -0.3                         | 12.0                              | 12.3                          |
| 0.027 | 0.0                            | -6.0                                | -6.0                            | -3.0                         | 3.0                               | 6.0                           |
| 0.036 | 4.3                            | -36.0                               | -40.3                           | -1.3                         | -9.0                              | -7.7                          |
| 0.045 | 11.3                           | -57.0                               | -68.3                           | 4.0                          | -27.0                             | -31.0                         |
| 0.054 | 41.3                           | -96.0                               | -137.3                          | 15.3                         | -42.0                             | -57.3                         |
| 0.063 | 25.6                           | -66.0                               | -91.6                           | 30.6                         | -63.0                             | -93.6                         |
| 0.072 | 17.6                           | 54.0                                | 36.4                            | 64.6                         | -51.0                             | -115.6                        |
| 0.081 | 11.3                           | 60.0                                | 48.7                            | 51.6                         | 45.0                              | -6.6                          |
| 0.090 | 15.3                           | 60.0                                | 44.7                            | 18.6                         | 0.0                               | -18.6                         |
| 0.099 | 17.0                           | 57.0                                | 40.0                            | 2.6                          | 0.0                               | -2.6                          |
| 0.108 | 14.0                           | 39.0                                | 25.0                            | -0.6                         | 0.0                               | 0.6                           |
| 0.117 | 5.6                            | 15.0                                | 9.4                             | -2.0                         | 0.0                               | 2.0                           |
| 0.126 | 1.5                            | 0.0                                 | -1.5                            |                              |                                   |                               |
| 0.135 | -1.0                           | -6.0                                | -5.0                            |                              |                                   |                               |
| 0.144 | -2.3                           | -9.0                                | -6.7                            |                              |                                   |                               |
| 0.153 | -3.3                           | -9.0                                | -5.7                            |                              |                                   |                               |

All measurements are given in units of 0.02 millivolt.  $V_F$  is the potential of the left leg.  $-V_5+V_F$  is the deflection in precordial Lead V as recorded.  $V_5$  is the potential of precordial point 5.

of the last precordial lead are of the same form up to the point where the chief upstroke occurs.

We have computed the potential variations of the point from which the last lead was taken. The numerical data are given in Table III. Although correction alters the form of the recorded ventricular complexes of this lead, it does not materially alter the amplitude or time of the chief upstroke.

CASE 6.—The subject was a man, aged sixty-two years, with hypertension (184/120), general arteriosclerosis, enlargement of the heart, and myocardial weakness. No valve lesions were present. The electrocardiogram showed bundle-branch block of the rare type with a QRS interval of 0.14 second. Five precordial leads were taken: (1) from the fifth costal cartilage at the right sternal edge; (2) from the fifth costal cartilage at the left sternal edge; (3) from the fifth intercostal space midway between the left sternal edge and the left midclavicular line; (4) from the fifth intercostal space 3 cm. medial to the anterior axillary line; (5) from the fifth intercostal space at the anterior axillary line. These curves are shown in Fig. 15.

In the first two leads the chief upstroke is late (0.097 second after the onset of R). In the third lead the ventricular complex is of small amplitude. In the last two leads the chief upstroke comes at the time that the peak of R is written and about 0.03 second earlier than the chief upstroke of the first two leads.

CASE 7.—The subject was a woman, aged thirty-two years, with mitral stenosis, who gave a history of rheumatic fever. There were no signs of cardiac failure; the heart was moderately enlarged. The electrocardiogram showed diphasic ventricular

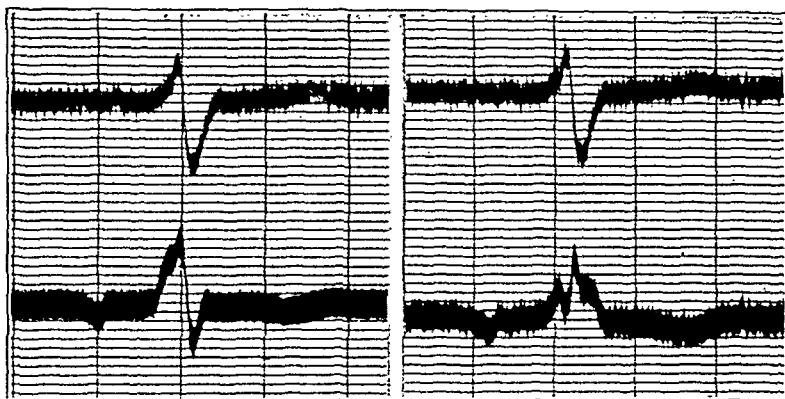


Fig. 14.—Case 6. Leads I and II on the left; Leads I and III on the right. Bundle branch block of the rare type with a QRS interval of 0.14 second.

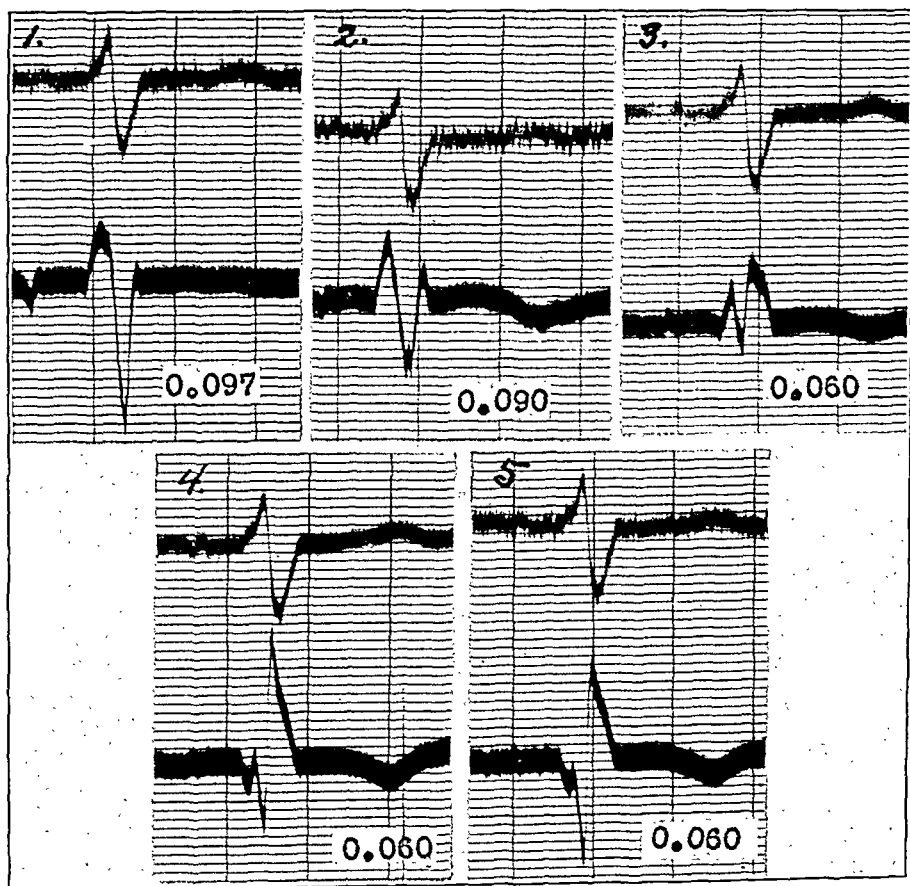


Fig. 15.—Case 6. A series of five precordial leads, each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 6 to 6.5 mm.

complexes with a QRS interval of 0.105 second. The complexes were not conspicuously notched, but were otherwise strongly suggestive of bundle-branch block of the rare type. Four precordial leads were taken: (1) from the third intercostal space near the right border of the sternum; (2) from the third intercostal space near the left border of the sternum; (3) from the fourth intercostal space 8.5 cm.

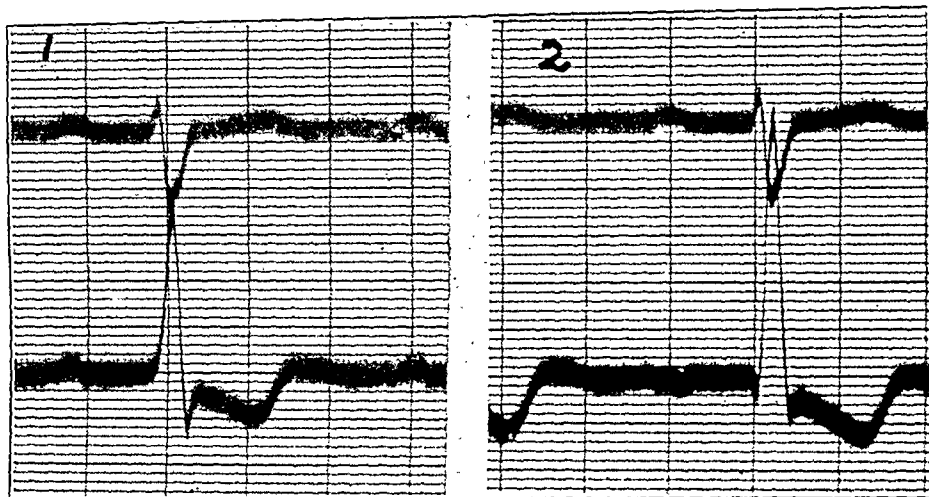


Fig. 16.—Case 7. Leads I and II on the left; Leads I and III on the right. Bundle-branch block of the rare type with a QRS interval of 0.105.

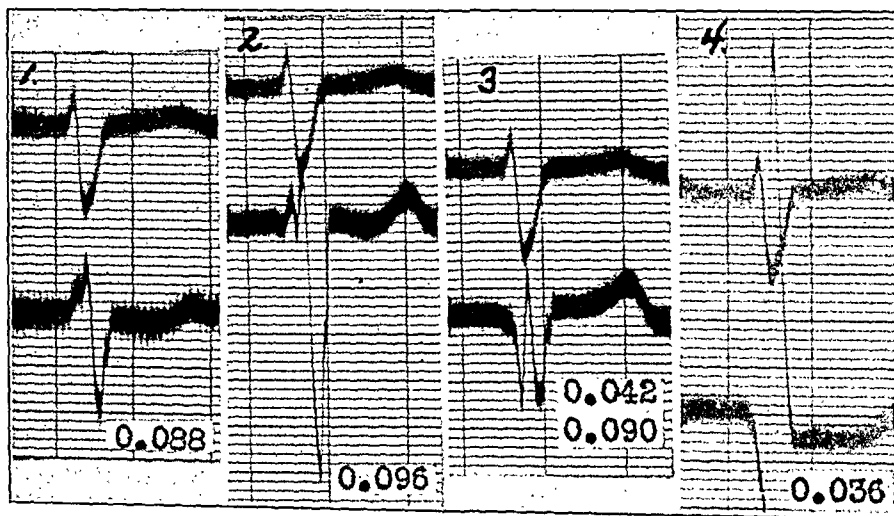


Fig. 17.—A series of four precordial leads each recorded simultaneously with Lead I. In the semidirect leads one millivolt produced a deflection of 5 mm. in Lead I, 9 mm. in Leads II and III. In the case of IV the standardization was not recorded on the film.

to the left of the midline; (4) from the sixth intercostal space near the anterior axillary line. These curves are shown in Fig. 17. In the first two leads, the chief ventricular upstroke is late. The ventricular complex of the third lead is of the transitional type with two principal upstrokes. In the last lead the chief upstroke is relatively early. We have computed the potential variations of the indifferent electrode (Table III); they are too small to alter materially the form of the ventricular complexes or the time or amplitude of the chief upstroke.

*Discussion.*—In all of the cases of bundle-branch block studied the first leads of the series taken, those from the right and central portions

of the precordium, have yielded ventricular complexes similar to those obtained in the cases described; the chief upstroke of these leads has always been early in the common type of branch block and late in the rare type. These complexes have always resembled those of Lead I in general outline. It should be noted that in so far as the potential variations of the indifferent electrode are effective, they tend to produce a ventricular complex of the opposite type.

The form of the complexes obtained by leading from points further to the left has, on the other hand, varied considerably. In branch block of the common type these complexes were sometimes of small amplitude, and showed no sharp deflections. Sometimes there was no deflection which could be regarded as a principal upstroke; when such a deflection could be recognized, it always occurred later than the chief upstroke of the earlier leads of the series, but it often rose so slowly as to make the evaluation of its significance difficult or impossible. It may have been in these cases that the exploring electrode was too far from the surface of the heart for our purpose, or that the investigation was not carried far enough to the left to enter the left ventricular field proper.

The three cases of bundle-branch block of the rare type which we have discussed are the only ones that we have had the opportunity of studying. It will be noted that although the chief upstrokes of the precordial leads taken from the left side of the precordium in this type of branch block are early in comparison with the chief upstrokes of leads from the right side of the precordium in the same subject, they are relatively late when compared with the earliest chief upstrokes obtained in branch block of the common type. This observation is consistent with the fact that the chief upstrokes obtained from the left side of the precordium are later than those obtained from the right side in cases in which the ventricular complex of the electrocardiogram is of the normal type. In most cases of bundle-branch block the heart is greatly hypertrophied. It cannot be assumed that the hypertrophy and the myocardial changes present are confined to the muscle of the homolateral ventricle. It is not surprising therefore that the earliest chief upstrokes obtained in cases of branch block are sometimes later than the chief upstrokes obtained by leading from the same part of the precordium in normal subjects.

When the complexes yielded by serial precordial leads in clinical bundle-branch block are compared with those obtained by serial semi-direct leads in experimental canine branch block, it is clear that the common type of clinical branch block must be left branch block, not right, and that the rare type of clinical branch block must be right, not left. This conclusion is in harmony with the form of the complexes obtained by Barker, Macleod, and Alexander<sup>9</sup> by electric stimulation of the exposed human heart.



It is hoped that serial precordial leads may aid in the solution of other problems, such as the location of the conduction defect in various types of intraventricular block, the order of ventricular excitation in ventricular hypertrophy, and certain problems connected with the T-deflection, particularly those which relate to the location of the infarcted area in coronary thrombosis. We do not wish, however, to give the impression that the curves obtained by this method of leading are always easy to interpret. We have found, for instance, that ventricular extrasystoles of the type in which the most prominent deflection of the ventricular complex is downward in Lead I and upward in Lead III do not always yield, as might be expected, results similar to those obtained in the rare type of branch block. Except for bundle-branch block, however, too few cases of any one type have been examined to permit any definite conclusions to be drawn at this time.

#### SUMMARY

Leads in which one electrode (the exploring electrode) is placed close to the heart and the other (the indifferent electrode) at a distance from it are semidirect leads. In experiments on dogs serial semidirect leads were taken from the surface of a pad of gauze soaked in warm normal salt solution and laid upon the exposed heart. The galvanometer connections were made in such a way that relative negativity of the exploring electrode yielded an upward deflection in the completed curve.

In animals in which bundle-branch block had been produced, the chief upstroke of the ventricular complex occurred early in those semidirect leads in which the exploring electrode was close to the surface of the contralateral, and late in those leads in which this electrode was close to the surface of the homolateral ventricle. In the former case the mean potential of the exploring electrode during the QRS interval was usually negative; in the latter case, usually positive.

In precordial leads the exploring electrode is placed on the precordium and the indifferent electrode on the left leg.

Serial precordial leads in cases of clinical bundle-branch block of the common type yield results similar to those obtained by semidirect leads in experimental left branch block. In the rare type of bundle-branch block they yield results similar to those obtained in experimental right branch block.

The common type of bundle-branch block is left branch block; the rare type, right branch block.

The chief ventricular upstroke of semidirect leads, in which the exploring electrode is placed close to the ventricular surface, corresponds to the intrinsic deflection of direct leads from the ventricles in which a single contact is placed upon the muscle.

We wish to thank Eli Lilly & Company for their kindness in supplying us with the sodium amytal used in our animal experiments.

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## THE TRANSVERSE DIAMETER OF THE HEART

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THE transverse diameter of the heart's shadow can be accurately measured by the x-ray and is both a satisfactory and a practical guide for estimating the size of the heart. The left auricle may enlarge without affecting the transverse diameter, but an increase in the size of any or all of the three remaining chambers will result in an increase in the measurement of this diameter. A definite decision as to whether or not a heart is enlarged can be made only if the transverse diameter is compared with some standard which will state what the diameter of the heart of an individual should be if that individual's heart were normal.

In 1919 Danzer<sup>1</sup> suggested the use of the cardiothoracic ratio as such a standard. According to this standard a heart is normal in size when its transverse diameter approximates one-half the internal diameter of the chest and is enlarged when its transverse diameter exceeds 50 per cent of the internal diameter of the chest. This theory is supported in papers by Jacobs and Worster<sup>2</sup> who also quote an affirmative opinion by Lee and Holmes, and by Martin.<sup>3</sup> None of these articles contains detailed data in support of the validity of this standard, and nowhere can one find a control study in which a group of normal individuals were examined. Smith and Blaedorn<sup>4</sup> hold a contrary opinion and contend that "any conclusion as to the relative size of the heart based on comparative dimensions, ratios or relations to body landmarks is fallacious and should be applied clinically with great reserve."

In 1926 Fred J. Hodges and J. A. E. Eyster<sup>5</sup> prepared a table for the prediction of the cardiac area and the transverse diameter in any normal adult male whose age, weight and height are known. The figures for the transverse diameter were derived from the formula  $TD = +0.1094 \times A - 0.1941 \times H + 0.8179 \times W + 95.8625$ , in which TD represents the transverse diameter, A the age, H the height and W the weight. The data were obtained from eighty subjects who showed no sign of cardiac abnormality. The measurements were made by orthodiagraphy. The authors concluded that if a heart is found to be 5 mm. wider in its greatest diameter as predicted by the formula the chances are three to one that the enlargement is pathological. A later article by Eyster<sup>6</sup> states that in one hundred more cases (no mention of sex) which have been added to the original series, 3 per cent exceeded the predicted transverse diameter by more than 10 per cent. A table based on the formula enables one to make a quick calculation of the predicted diameter for

any case and to dispense with the use of the formula which is too cumbersome and time consuming for ordinary clinical work. For the mathematical details the authors' papers should be consulted.

It must be emphasized that the table of Hodges and Eyster is applicable to measurements obtained by orthodiagraphy only and not to those obtained by teleroentgenography. The measurement of the transverse diameter in the teleroentgenogram is always greater than the actual width. This excess varies in different individuals, the divergence of the rays being influenced largely by two factors, the size of the heart and the distance that the heart lies from the anterior chest wall and therefore from the x-ray plate. Paul D. White in his recent volume on *Heart Disease* estimates that in the teleroentgenogram the error of excess for the transverse diameter is from 0.5 cm. to 1.5 cm. (4 per cent to 12 per cent) in normal hearts and in pathological hearts as much as 2.0 cm. In orthodiagraphy there are no such sources of error because only the direct central ray is used in outlining the heart.

The technic employed in the present study was as follows: The position of the central ray is determined and the site marked by a circular dot made with a black lead pencil. This is more convenient than a lead marker and is just as clearly seen. The patient breathing quietly stands in front of the screen, the black dot, i.e., the central ray is made to follow the outline of the heart and the tracing is recorded by means of a side arm which moves synchronously with the tube and the screen. It is important that the screen be moved only in the one vertical plane. Otherwise the central ray will change its position and nullify accurate results. For purpose of control the furthestmost points on the left and right borders are again marked, and if they correspond with similar points on the tracing, one has reasonable assurance of the correctness of the findings. Occasionally an accurate record cannot be made because of the obscurity of the apex during quiet respiration. Deep inspiration may visualize such an apex, but it also lengthens the heart and narrows the transverse diameter, which make it inapplicable in this investigation.

In the present study the actual transverse diameters found in one hundred noncardiac males are compared with the predicted transverse diameters of Hodges and Eyster for these same individuals. The measurements of one-half the internal diameter of the chest also were obtained in ninety-seven of these one hundred cases and compared with the actual transverse diameters. The tabulations of these figures should enable one to test the validity of either standard and to compare the values of each.

Seventy-five women also were examined and their cardiac transverse diameters studied in a similar manner.

These 175 individuals comprise a successive number of ambulatory noncardiac patients who presented an opportunity for orthodiagraphic study. None showed any evidence of heart disease or any signs or symp-

TABLE I  
NONCARDIAC MALES

| NO. | AGE | WEIGHT<br>KILOS | HEIGHT<br>CM. | TRANSVERSE<br>DIAMETER | PREDICTED<br>DIAMETER OF<br>HODGES & EYSTER | ONE-HALF INTERNAL<br>DIAMETER OF CHEST |
|-----|-----|-----------------|---------------|------------------------|---|--|
| 1   | 41  | 55              | 171           | 10.6                   | 11.1  | 11.8                                   |
| 2   | 55  | 70              | 172           | 13.8                   | 12.6  | 11.5                                   |
| 3   | 49  | 56              | 168           | 11.6                   | 11.3  | 11.9                                   |
| 4   | 32  | 67              | 169           | 12.1                   | 12.1  | —                                      |
| 5   | 53  | 68              | 168           | 12.1                   | 12.4  | 12.2                                   |
| 6   | 42  | 66              | 179           | 11.7                   | 11.8  |  |
| 7   | 61  | 65              | 168           | 10.9                   | 12.1  | 12.7                                   |
| 8   | 43  | 79              | 178           | 13.9                   | 13.0  | 13.2                                   |
| 9   | 36  | 87              | 183           | 14.1                   | 13.5  | 14.5                                   |
| 10  | 43  | 76              | 174           | 12.3                   | 12.8  | 12.5                                   |
| 11  | 29  | 98              | 187           | 13.4                   | 14.2  | 13.0                                   |
| 12  | 58  | 84              | 166           | 14.1                   | 13.7  | 12.0                                   |
| 13  | 19  | 61              | 168           | 10.6                   | 11.5  |  |
| 14  | 23  | 62              | 174           | 11.5                   | 11.5  | 12.0                                   |
| 15  | 54  | 65              | 164           | 12.9                   | 12.2  | 11.7                                   |
| 16  | 23  | 64              | 171           | 10.0                   | 10.9  | 12.0                                   |
| 17  | 28  | 55              | 178           | 11.5                   | 10.8  | 12.5                                   |
| 18  | 31  | 63              | 169           | 10.8                   | 11.7  | 11.0                                   |
| 19  | 51  | 70              | 161           | 12.2                   | 12.6  | 12.7                                   |
| 20  | 46  | 60              | 169           | 12.9                   | 11.6  | 11.7                                   |
| 21  | 35  | 55              | 163           | 11.0                   | 11.2  | 11.8                                   |
| 22  | 42  | 77              | 170           | 14.4                   | 13.0  | 12.7                                   |
| 23  | 47  | 80              | 177           | 15.0                   | 13.1  | 13.2                                   |
| 24  | 22  | 65              | 178           | 12.3                   | 11.9  | 13.0                                   |
| 25  | 54  | 78              | 179           | 12.0                   | 12.9  | 12.2                                   |
| 26  | 53  | 77              | 173           | 13.3                   | 13.0  | 12.6                                   |
| 27  | 28  | 60              | 178           | 10.3                   | 11.2  | 11.9                                   |
| 28  | 32  | 69              | 183           | 10.5                   | 12.0  | 12.7                                   |
| 29  | 46  | 86              | 176           | 13.7                   | 13.6  | 12.7                                   |
| 30  | 44  | 93              | 180           | 14.0                   | 14.1  | 12.7                                   |
| 31  | 51  | 74              | 173           | 12.7                   | 12.8  | 13.1                                   |
| 32  | 42  | 77              | 166           | 14.2                   | 13.0  | 12.0                                   |
| 33  | 57  | 87              | 175           | 13.8                   | 13.8  | 12.1                                   |
| 34  | 23  | 67              | 178           | 12.1                   | 11.9  | 12.7                                   |
| 35  | 60  | 67              | 167           | 12.4                   | 11.3  | 11.2                                   |
| 36  | 28  | 63              | 170           | 11.7                   | 11.6  | 12.0                                   |
| 37  | 46  | 59              | 170           | 11.1                   | 11.6  | 11.7                                   |
| 38  | 42  | 78              | 178           | 13.3                   | 12.9  | 12.3                                   |
| 39  | 44  | 60              | 169           | 11.2                   | 11.7  | 11.5                                   |
| 40  | 31  | 69              | 178           | 11.4                   | 12.0  | 11.7                                   |
| 41  | 46  | 86              | 178           | 13.9                   | 13.6  | 12.5                                   |
| 42  | 53  | 70              | 169           | 12.2                   | 12.5  | 11.2                                   |
| 43  | 29  | 91              | 170           | 14.6                   | 13.9  | 13.4                                   |
| 44  | 19  | 71              | 168           | 12.2                   | 12.1  | 12.5                                   |
| 45  | 28  | 69              | 170           | 11.6                   | 12.0  | 12.5                                   |
| 46  | 39  | 61              | 179           | 12.2                   | 11.5  | 13.0                                   |
| 47  | 28  | 55              | 173           | 10.8                   | 10.9  | 12.2                                   |
| 48  | 27  | 70              | 185           | 12.0                   | 11.9  | 12.7                                   |
| 49  | 50  | 88              | 191           | 14.2                   | 13.6  | 14.0                                   |
| 50  | 27  | 65              | 176           | 12.0                   | 11.7  | 13.1                                   |
| 51  | 30  | 84              | 158           | 13.1                   | 13.4  | 12.8                                   |
| 52  | 31  | 58              | 170           | 9.9                    | 11.3  | 13.0                                   |
| 53  | 19  | 65              | 181           | 10.5                   | 11.6  | 11.8                                   |
| 54  | 26  | 54              | 172           | 10.0                   | 10.8  | 12.6                                   |
| 55  | 51  | 71              | 174           | 11.4                   | 12.5  | 11.0                                   |

TABLE I (CONTINUED)

## NONCARDIAC MALES

| NO.          | AGE   | WEIGHT<br>KILOS | HEIGHT<br>CM. | TRANSVERSE<br>DIAMETER | PREDICTED<br>DIAMETER OF<br>HODGES & EYSTER | ONE-HALF INTERNAL<br>DIAMETER OF CHEST |
|--------------|-------|-----------------|---------------|------------------------|---|--|
| 601          | 28    | 62              | 165           | 11.3                   | 11.6  | 11.7                                   |
| 602          | 18    | 55              | 179           | 11.4                   | 10.9  | 12.5                                   |
| 56           | 22    | 56              | 176           | 10.4                   | 11.0  | 13.0                                   |
| 57           | 29    | 64              | 179           | 10.2                   | 11.5  | 12.6                                   |
| 58           | 33    | 60              | 173           | 11.3                   | 11.4  | 12.0                                   |
| 59           | 18    | 64              | 175           | 11.8                   | 11.5  | 12.0                                   |
| 60           | 19    | 62              | 184           | 10.5                   | 11.2  | 11.7                                   |
| 61           | 43    | 74              | 165           | 13.4                   | 12.8  | 12.0                                   |
| 62           | 30    | 72              | 178           | 11.2                   | 12.3  | 13.3                                   |
| 63           | 31    | 77              | 172           | 13.0                   | 12.8  | 13.0                                   |
| 64           | 33    | 90              | 179           | 13.2                   | 13.7  | 12.5                                   |
| 65           | 18    | 60              | 183           | 10.8                   | 11.0  | 12.9                                   |
| 66           | 23    | 67              | 173           | 12.0                   | 11.9  | 13.0                                   |
| 67           | 21    | 72              | 175           | 10.8                   | 12.2  | 12.1                                   |
| 68           | 41    | 59              | 168           | 11.6                   | 11.5  | 11.6                                   |
| 69           | 31    | 72              | 181           | 12.7                   | 12.2  | 11.8                                   |
| 70           | 43    | 66              | 170           | 11.9                   | 12.1  | 11.0                                   |
| 71           | 58    | 66              | 180           | 12.1                   | 12.0  | 12.7                                   |
| 72           | 48    | 70              | 181           | 12.0                   | 12.2  | 12.7                                   |
| 73           | 30    | 61              | 167           | 10.9                   | 11.6  | 11.5                                   |
| 74           | 35    | 55              | 162           | 11.1                   | 11.2  | 11.7                                   |
| 75           | 44    | 63              | 181           | 11.1                   | 11.4  | 12.8                                   |
| 76           | 21    | 71              | 178           | 11.2                   | 12.1  | 12.3                                   |
| 77           | 35    | 91              | 168           | 13.5                   | 14.0  | 12.8                                   |
| 78           | 30    | 70              | 176           | 12.3                   | 12.2  | 12.7                                   |
| 79           | 29    | 80              | 183           | 12.2                   | 12.2  | 13.0                                   |
| 80           | 33    | 76              | 178           | 11.0                   | 12.6  | 11.8                                   |
| 81           | 17    | 50              | 165           | 9.8                    | 10.5  | 10.8                                   |
| 82           | 41    | 80              | 174           | 13.4                   | 13.1  | 13.0                                   |
| 83           | 60    | 56              | 168           | 11.9                   | 11.4  | 11.0                                   |
| 84           | 34    | 74              | 180           | 11.9                   | 12.5  | 13.6                                   |
| 85           | 34    | 78              | 173           | 13.1                   | 12.9  | 12.3                                   |
| 86           | 37    | 55              | 168           | 12.4                   | 11.1  | 11.7                                   |
| 87           | 26    | 81              | 177           | 12.3                   | 13.0  | 13.1                                   |
| 88           | 46    | 70              | 171           | 12.7                   | 12.4  | 12.6                                   |
| 89           | 45    | 75              | 163           | 13.1                   | 12.9  | 11.1                                   |
| 90           | 19    | 58              | 171           | 10.6                   | 11.1  | 11.7                                   |
| 91           | 47    | 49              | 156           | 11.0                   | 10.9  | 11.7                                   |
| 92           | 25    | 73              | 179           | 12.9                   | 12.6  | 12.6                                   |
| 93           | 49    | 70              | 175           | 12.4                   | 12.3  | 12.2                                   |
| 94           | 50    | 94              | 171           | 15.5                   | 14.5  | 13.0                                   |
| 254          | 24    | 59              | 179           | 10.6                   | 11.0  | 12.5                                   |
| 256          | 60    | 88              | 176           | 13.3                   | 13.8  | 12.2                                   |
| 257          | 41    | 67              | 166           | 12.5                   | 12.2  | 12.5                                   |
| 260          | 25    | 86              | 174           | 13.3                   | 13.4  | 11.8                                   |
| Total        | 3671  | 6961            | 17345         | 1213.6                 | 1221.5                                      | 1195.1                                 |
| Aver-<br>age | 36.71 | 69.61           | 173.45        | 12.13                  | 12.21                                       | 12.32                                  |

toms referable to the heart. No case was excluded on account of the size of the heart alone, because it was thought that the exclusion of an apparently large or small heart would be unjustified in an investigation which is concerned principally with the size of the heart in normal

persons. The position of the heart, whether vertical or horizontal, was not given consideration because it was felt that these positions are not abnormal, but probably are to a large extent characteristic of an individual's physique.

# TRANSVERSE DIAMETER OF THE MALE HEART

In Table I the detailed figures of one hundred male subjects are recorded, giving for each the age, the weight, the height, the transverse diameter found, the predicted transverse diameter of Hodges and Eyster and the measurement of one-half the internal diameter of the chest.

Table II is presented to show that this group of 100 cases is comparable with Hodges and Eyster's group of 80 cases.

TABLE II

|                 |                    | AGE   | HEIGHT | WEIGHT | TD    |
|-----------------|--------------------|-------|--------|--------|-------|
| Hodges & Eyster | 80 cases—Averages  | 31.10 | 175.46 | 69.162 | 12.17 |
| Present series  | 100 cases—Averages | 36.71 | 173.45 | 69.61  | 12.13 |

Table III presents in round numbers a summary of the variations found in Table I. The cases are arranged in groups in accordance with the amount of the variation of the actual transverse diameter from the prediction figures of Hodges and Eyster and from the figures which represent one-half the internal diameter of the chest. For purposes of comparison the groups are bracketed.

TABLE III

| VARIATION CM.                                | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5   | 0   | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | CM. |
|--|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|
| From prediction figures of Hodges and Eyster |     |     |     |     | 1.  | 8   | 15    | 30  | 3   | 28  | 9   | 5   | 1   |     |
|  |     |     |     |     | 24% |     |       | 61% |     |     | 15% |     |     |     |
| From 1/2 internal diameter of chest          | 1   | 2   | 4   | 6   | 9   | 19  | 15    | 3   | 9   | 12  | 9   | 4   | 4   |     |
|  | 42% |     |     |     |     |     | 27.5% |     |     | 30% |     |     |     |     |

Explanation of Table III: zero represents the standard and the figures beneath it the number of hearts which had exactly the same transverse diameter as that estimated by the standards. The figures to the right of zero represent the distances in centimeters above the standard and the figures to the left similar distances below the standards. The number of hearts which showed any variation are tabulated in accordance with the amount of the variation, e.g., in twenty-eight hearts the actual transverse diameter exceeded the predicted diameter by 0.5 cm. or less, in nine the excess was between 0.5 cm. and 1.0 cm., in five between 1.0 cm.

TABLE IV  
NONCARDIAC FEMALES

| NUMBER | AGE | WEIGHT KILOS. | HEIGHT CM. | TRANSVERSE DIAMETER | HODGES & EYSTER PREDICTED FIGURES FOR MALES | PREDICTED FIGURES ADJUSTED FOR FEMALES; MALE FIGURE MINUS 0.8 CM. | ONE-HALF INTER-NAL DIAMETER OF CHEST |
|--------|-----|---------------|------------|---------------------|---|---|--------------------------------------|
| 95     | 23  | 37            | 146        | 9.9                 | 9.9   | 9.1   | 10.1                                 |
| 96     | 68  | 59            | 167        | 11.6                | 11.6  | 10.8  | 10.1                                 |
| 97     | 44  | 42            | 146        | 9.2                 | 10.7  | 9.9   | 11.1                                 |
| 98     | 47  | 52            | 163        | 10.1                | 11.0  | 10.2  | 10.2                                 |
| 99     | 17  | 46            | 157        | 9.1                 | 10.3  | 9.5   | 9.8                                  |
| 100    | 28  | 52            | 158        | 9.8                 | 10.6  | 9.8   | 11.1                                 |
| 101    | 23  | 62            | 162        | 10.5                | 11.7  | 10.9  | 11.0                                 |
| 102    | 18  | 51            | 166        | 9.3                 | 10.6  | 9.8   | 12.0                                 |
| 103    | 31  | 56            | 158        | 11.5                | 11.4  | 10.6  | 11.1                                 |
| 104    | 27  | 45            | 157        | 9.9                 | 10.3  | 9.6   | 10.7                                 |
| 105    | 30  | 79            | 165        | 11.2                | 12.9  | 12.1  | 11.6                                 |
| 106    | 33  | 57            | 155        | 10.4                | 11.2  | 10.4  | 10.0                                 |
| 107    | 39  | 77            | 163        | 12.6                | 13.0  | 12.2  | 11.5                                 |
| 108    | 31  | 64            | 147        | 11.5                | 12.2  | 11.4  | 10.7                                 |
| 109    | 24  | 47            | 164        | 9.7                 | 10.0  | 9.2   | 10.6                                 |
| 110    | 30  | 62            | 163        | 10.7                | 11.7  | 10.9  | 10.5                                 |
| 111    | 31  | 44            | 165        | 9.1                 | 10.2  | 9.4   | 11.2                                 |
| 112    | 42  | 58            | 159        | 10.9                | 11.6  | 10.8  | 10.6                                 |
| 113    | 37  | 45            | 151        | 9.1                 | 10.7  | 9.9   | 10.2                                 |
| 114    | 22  | 46            | 168        | 9.7                 | 10.1  | 9.3   | 12.0                                 |
| 115    | 36  | 65            | 163        | 10.0                | 12.0  | 11.2  | 10.9                                 |
| 116    | 16  | 58            | 170        | 10.5                | 11.1  | 10.3  | 11.8                                 |
| 117    | 28  | 56            | 163        | 10.8                | 11.2  | 10.4  | 11.0                                 |
| 118    | 24  | 48            | 164        | 9.4                 | 10.4  | 9.6   | 11.5                                 |
| 119    | 22  | 48            | 163        | 10.5                | 10.4  | 9.6   | 11.5                                 |
| 120    | 33  | 57            | 152        | 9.8                 | 11.6  | 10.8  | 11.0                                 |
| 121    | 50  | 67            | 159        | 11.8                | 12.5  | 11.7  | 10.8                                 |
| 122    | 27  | 63            | 173        | 10.3                | 11.6  | 10.8  | 11.1                                 |
| 123    | 35  | 52            | 160        | 9.4                 | 11.0  | 10.2  | 11.5                                 |
| 124    | 24  | 55            | 165        | 10.2                | 11.1  | 10.3  | 11.5                                 |
| 125    | 26  | 60            | 164        | 11.6                | 11.5  | 10.7  | 12.1                                 |
| 126    | 36  | 74            | 162        | 11.5                | 12.8  | 12.0  | 11.2                                 |
| 127    | 36  | 54            | 163        | 10.6                | 11.1  | 10.3  | —                                    |
| 128    | 40  | 63            | 159        | 10.8                | 12.0  | 11.2  | —                                    |
| 129    | 24  | 77            | 165        | 12.4                | 12.9  | 12.1  | 11.6                                 |
| 130    | 32  | 68            | 159        | 11.2                | 12.3  | 11.5  | 12.0                                 |
| 230    | 34  | 63            | 161        | 11.3                | 11.9  | 11.1  | 10.5                                 |
| 132    | 27  | 83            | 168        | 10.7                | 13.3  | 12.5  | 10.2                                 |
| 133    | 33  | 73            | 162        | 11.4                | 12.7  | 11.9  | 11.6                                 |
| 134    | 41  | 61            | 163        | 11.4                | 11.7  | 10.9  | 11.1                                 |



In this series of one hundred male subjects the transverse diameter of the heart was found to be within 0.5 cm. of the predicted figures in 61 per cent. Only 27 per cent fell within 0.5 cm. of the measurement of one-half the internal diameter of the chest.

In the group in which the question of enlargement arises, those hearts which are wider than the standard by more than 0.5 cm., 15 per cent of these supposedly normal hearts would be considered enlarged according to the prediction figures and 30 per cent when one-half the internal diameter is used as a standard.

Twenty-four per cent of the hearts are small, i.e., the transverse diameter is less than the standard of Hodges and Eyster by more than 0.5 cm. In a corresponding bracket for one-half the internal diameter the figure is 42 per cent.

This table presents a comparison showing that the transverse diameter found approximates the predicted figures of Hodges and Eyster in a far greater percentage than it does the measurement of one-half the internal diameter of the chest. In fact the latter measurement is found to vary from the actual diameter in such a large percentage of cases that it is of questionable value as a standard in estimating abnormality in the size of a heart.

#### TRANSVERSE DIAMETER OF THE FEMALE HEART

The prediction table of Hodges and Eyster was prepared from data obtained in the examination of male subjects only. Table IV shows that this standard is not applicable to this group of 75 women. However, by reducing the predicted transverse diameter for men by 0.8 cm. a standard for women is obtained. By the use of this adjusted standard it was found that the actual transverse diameter in the female varied from the adjusted prediction figures to a degree which is practically the same as the results obtained in the examination of the male subjects.

A comparison of the variations in the male and female groups is seen in Table V.

TABLE V

| VARIATION                                 | 2.0   | 1.5 | 1.0 | 0.5 | 0 | 0.5 | 1.0   | 1.5 | 2.0 | CM. |
|---|-------|-----|-----|-----|---|-----|-------|-----|-----|-----|
| From prediction figures of 100 males      | 1     | 8   | 15  | 30  | 3 | 28  | 9     | 5   | 1   |     |
|   | 24%   |     |     | 61% |   |     | 15%   |     |     |     |
| From suggested female standard (75 cases) | 1     | 5   | 11  | 16  | 6 | 23  | 12    | 1   |     |     |
|   | 22.7% |     |     | 60% |   |     | 17.3% |     |     |     |

It is evident from Table V that in this group of 75 female subjects the transverse diameter of the heart is smaller by 0.8 cm. than the transverse diameter in a male subject of the same age, weight and height.

Table VI which is arranged in the same way as Tables III and V shows that as in the male group, the measurement of one-half the internal diameter of the chest varies from the actual transverse diameter in such a large percentage of cases that it cannot be used as a satisfactory guide in judging abnormalities of the size of the female heart.

TABLE VI

| VARIATION IN FEMALES CM.         | 3.0 | 2.5 | 2.0 | 1.5   | 1.0 | 0.5 | 0     | 0.5 | 1.0 | 1.5   | 2.0 |
|----------------------------------|-----|-----|-----|-------|-----|-----|-------|-----|-----|-------|-----|
| From adjusted prediction figures |     |     |     | 1     | 5   | 11  | 16    | 6   | 23  | 12    | 1   |
|                                  |     |     |     | 22.7% |     |     | 60%   |     |     | 17.3% |     |
| From one-half internal diameter  | 1   | 6   | 2   | 10    | 11  | 13  | 1     | 14  | 10  | 4     | 1   |
|                                  |     |     |     | 41%   |     |     | 38.5% |     |     | 20.5% |     |

## COMBINED GROUPS: MALE AND FEMALE

Using the prediction table of Hodges and Eyster for males and the adjusted prediction figures for females Table VII shows the amount of variation from the standards for these 175 individuals in whom there was no reason for suspecting heart disease.

TABLE VII

| TABLE VII     |       |     |     |       |   |     |     |     |     |
|---------------|-------|-----|-----|-------|---|-----|-----|-----|-----|
| VARIATION CM. | 2.0   | 1.5 | 1.0 | 0.5   | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| 175 cases     | 2     | 13  | 26  | 46    | 9 | 51  | 21  | 6   | 1   |
|               | 23.5% |     |     | 60.5% |   |     | 16% |     |     |
|               | 87%   |     |     |       |   |     |     |     |     |

It is seen from Table VII that the actual transverse diameter of the heart in 175 cases was found to be within 0.5 cm. of the predicted diameter in 60.5 per cent of the cases, and within 1.0 cm. in 87 per cent. It was found larger by more than 0.5 cm. in 16 per cent and smaller by more than 0.5 cm. in 23.5 per cent. In this group which varies from the predicted figures by more than 0.5 cm. seven hearts, or 4 per cent of the total, were larger by more than 1.0 cm.; and fifteen hearts, or 8.5 per cent, were smaller by the same margin. If these findings are supported by further studies, it is suggested that a heart found to be within 0.5 cm. of the predicted figures be considered normal in size. Expressed in another way the average range in size of the transverse diameter of the normal heart is within 0.5 cm. of the predicted figures.

The twenty-eight hearts, or 16 per cent, which are larger by more than 0.5 cm. offer an opportunity for some speculation. Twenty-one hearts

(12 per cent) are larger than the standard by more than 0.5 cm., but by less than 1.0 cm. Whether or not they should be considered enlarged is a question which should remain open for the present. The seven hearts (4 per cent) which are greater by more than 1.0 cm. in their transverse diameter probably should be considered definitely enlarged. Whether or not they are pathologically enlarged is uncertain, because, as previously stated, we have been studying only the transverse diameter of hearts which otherwise showed no abnormality and have excluded none because of size alone. It is suggested, however, that enlargement of the degree found in these seven subjects even in the absence of other signs is a definite enough abnormality to justify the diagnosis of "possible heart disease."

#### COMMENT

It is doubtful whether a more exact standard can be devised for estimating clinically the diameter of the human heart, which necessarily varies in size and capacity under physiological conditions. Hodges and Eyster, however, suggest that greater accuracy might be obtained by employing another variable in addition to age, weight and height. If so it might be possible to reduce the percentages of hearts smaller by more than 0.5 cm., 24 per cent for males and 22.7 per cent for females, to still lower figures. But even here the variation is not pronounced, as only 9 per cent of the male and 8 per cent of the female hearts are smaller by more than 1.0 cm.

It is worthy of note in considering the margin of error in the practical application of the prediction figures of Hodges and Eyster that in this series of 175 noncardiac individuals the actual transverse diameter varies from the standard (using the adjusted standard for females) by more than 1.0 cm. in only 13 per cent, 4 per cent being larger and 9 per cent smaller.

The tables represent data obtained by orthodiagraphy and therefore are not applicable to the measurements by teleroentgenography. The articles previously referred to in this paper deal with the use of the cardiothoracic ratio in the teleroentgenogram only and not in the orthodiagram. The literature contains no study of the application of this ratio to the orthodiagram. Nevertheless it has been used quite frequently in estimating variation in the heart's size as measured by orthodiagraphy.

If, as the present study indicates, the cardiothoracic ratio is not applicable to orthodiagraphic measurements, which are exact, it is somewhat difficult to understand how this ratio can be an index of size in the teleroentgenogram where there are certain inherent errors which vary with each individual patient.

These same errors will make it difficult to adjust the standard of Hodges and Eyster so that it may be applied to the measurements obtained in teleroentgenography.

## CONCLUSIONS

The prediction table of Hodges and Eyster is a fairly satisfactory guide in enabling an examiner to judge abnormality in the size of the male heart and to estimate the degree of enlargement.

The adjusted standard for females in which the figures for males is reduced by 0.8 cm. is equally satisfactory.

One-half the internal diameter of the chest in the orthodiagram is a measurement which does not approximate the actual transverse diameter of the normal heart often enough to have much value as a standard guide.

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## THE DIURETIC EFFECT OF DIGITALIS\*

E. LEROY KELLUM, M.D.†

ROCHESTER, MINN.

WILLIAM WITHERING<sup>27</sup> in his original communication concerning the action of digitalis chiefly stressed the diuretic action of the drug. It is true he stated "it has a power over the motion of the heart to a degree yet unobserved in any other medicine and this power may be converted to salutary ends" but the main emphasis has to do with "a new diuretic which though not infallible" he believed to be "much more certain than any in present use" and "that it will often produce this effect after every other probable medicine has been fruitlessly tried." However, there has not been unanimous agreement with this observation of the excellent diuretic effect of digitalis. Germain<sup>10</sup> and Winogradoff<sup>26</sup> denied that digitalis possesses diuretic properties, and stated that the diuresis which often follows when an amelioration of the condition of the circulation has been produced by it in organic disease of the heart is only a mediate effect resulting from a return of the circulation to its normal condition. Among those who observed the diuretic effect of digitalis may be mentioned Christian,<sup>5</sup> Andrall and Christian and Lemaitre, and Brunton.<sup>4</sup> Brunton, in experiments on himself and other human subjects, concluded that digitalis acts as a diuretic in anasarca, especially if the anasarca is caused by heart disease, and that it sometimes, but not always, acts as such even in health. This observer further stated, "when digitalis acts upon the normal man so as to produce diuresis, the drain of fluid becomes so great, as I have found in my experiments, the thirst it induces becomes intolerable." Joerg<sup>14</sup> who carried out experiments on several healthy men, women, and children, found the output of urine increased with only one exception. Stadion,<sup>22</sup> after putting himself on a diet of weighed food and after determining the normal amount of his urine, took digitalin for eighteen days, beginning with 2 mg., and daily increasing the dose by 1 mg. At the conclusion of the experiment his urine had diminished in quantity.

Peculiarly little notice was paid to the original work of Withering for more than one hundred years, although in this period there were such outstanding teachers of conditions of the heart as Hope, Stokes, and Austin Flint. Physicians relied on other diuretics than digitalis to combat the edema of cardiac failure. MacKenzie<sup>18</sup> was the first

\*Read before the American Society of Clinical Investigation, Atlantic City, New Jersey, May 4, 1931. Work done in the Division of Medicine, The Mayo Clinic, under the supervision of Dr. Norman M. Keith.

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clinician to demonstrate conclusively the correctness of Withering's observations and instructions regarding the uses and administration of digitalis. Since MacKenzie's contributions, there has accumulated a vast literature on digitalis and much has been written about its effect.

One is impressed with the amount of study of this drug, and with the relatively few carefully controlled and standardized studies both of the healthy human subject and of patients with cardiac failure and edema. Few investigations have fulfilled the essential requirements of a preliminary period of control for the healthy human subject, or for patients with cardiac failure, of a preliminary period of absolute bodily rest; a constant diet of weighed food of known low water and low mineral content; daily extra intake of fluid of constant and carefully measured amount, and daily estimation of the output of urine, of body weight, of pulse rate, of blood pressure and of symptoms of the effect of digitalis.

However, there have appeared several excellent studies of the diuretic effect of digitalis in cases of myocardial failure with congestion and edema. Examples of such contributions are those of Cohn,<sup>6</sup> West and Pratt,<sup>23</sup> and Pratt<sup>20</sup> Eggleston,<sup>8</sup> Fraser,<sup>9</sup> Jensen,<sup>13</sup> Luten,<sup>17</sup> Christian,<sup>5</sup> Marvin<sup>10</sup> and Hay, Jones and Ince.<sup>11</sup> There is general agreement among these workers that when edema is present, either apparent or masked, it is usual for definite diuresis to occur under the influence of digitalis. If, however, edema is absent, they find no diuretic effect. This diuretic effect, in cases of heart failure and edema, they believe depends chiefly on the action of digitalis on the heart muscle alone. They further assumed that the fall in urinary output toward the end of treatment is due to diminished intake of fluid, associated with nausea and anorexia resulting from toxic symptoms of the drug. The diuretic effect was observed in cases with normal cardiac rhythm, as well as in cases with fibrillation of the auricles. It has also been shown that in establishing a sufficient basis for the study of such diuretic effect one must take into consideration the presence or absence of hypertension, the etiologic classification of heart disease, the stage of heart failure, and the dosage, potency, and rapidity of administration of the drug.

In treating cases of cardiac failure with considerable edema, Bannick, N. M. Keith and I not infrequently noted failure to produce satisfactory diuresis with digitalis. In such cases we were frequently able to obtain excellent diuresis by employing other diuretics. Willis<sup>24</sup> has reported a similar experience with other diuretics. Because of this experience the present work was attempted to determine the diuretic effect of digitalis both on the healthy human subject and in cases of heart failure with edema.

TABLE I  
DIETS USED IN THESE EXPERIMENTS

| SUBJECT OR PATIENT          | DIAGNOSIS      | AGE,<br>YEARS,<br>SEX | 1931                 | CARBOHY-<br>DRATES,<br>GM. | PRO-<br>TEINS,<br>GM. | FAT,<br>GM. | TOTAL<br>CALORIES | WATER,<br>C.C. | SODIUM<br>CHLO-<br>RIDE,<br>GM. |
|-----------------------------|----------------|-----------------------|----------------------|----------------------------|-----------------------|-------------|-------------------|----------------|---------------------------------|
| DIET FOR NORMAL SUBJECTS    |                |                       |                      |                            |                       |             |                   |                |                                 |
| Subject 1<br>(experiment 1) | Normal subject | 32 M                  |                      | 230                        | 60                    | 88          | 2000              | 820            | 1.5                             |
| Subject 1<br>(experiment 2) | Normal subject | 32 M                  | 10/27 to<br>11/ 1 to | 31 160<br>7 152            | 60<br>59              | 106<br>79   | 1800<br>1500      | 1180<br>1150   | 3.3<br>3.0                      |
| Subject 1<br>(experiment 3) | Normal subject | 32 M                  | .                    | 124 to 164                 | 56 to 59              | 62 to 90    | 1320 to 1495      | 860            | 1.4                             |
| Subject 2                   | Normal subject | 31 M                  |                      | 230                        | 60                    | 88          | 2000              | 820            | 1.5                             |
| Subject 3                   | Normal subject | 26 M                  |                      | 230                        | 60                    | 88          | 2000              | 820            | 1.5                             |

TABLE I (CONTINUED)

| SUBJECT OR PATIENT                         | DIAGNOSIS   | AGE,<br>YEARS,<br>SEX | 1931        | CARBOHY-<br>DRATES,<br>GM. | PRO-<br>TEINS,<br>GM. | FAT,<br>GM. | TOTAL<br>CALORIES | WATER,<br>C.C. | SODIUM<br>CHLO-<br>RIDE,<br>GM. |
|--|---|-----------------------|-------------|----------------------------|-----------------------|-------------|-------------------|----------------|---------------------------------|
| DIETS FOR PATIENTS WITH MYOCARDIAL FAILURE |   |                       |             |                            |                       |             |                   |                |                                 |
| Patient 1<br>(first admission)             | Rheumatic mitral endocarditis<br>with stenosis                          | 34 F                  | 4/ 5 to 17  | 168 to 231                 | 32 to 40              | 71 to 92    | 1440 to 2000      | 640 to 830     | 1.0                             |
| (second admission)                         |   |                       | 4/18 to 20  | 200 to 222                 | 46 to 49              | 111 to 123  | 2000 to 2200      | 760 to 820     | 1.1                             |
| 2  | Arteriosclerosis; essential hy-<br>pertension                           | 45 M                  | 4/ 5 to 12  | 200 to 243                 | 27 to 40              | 73 to 86    | 1740 to 1900      | 760 to 830     | 1.0                             |
| 3  | Questionable coronary sclero-<br>sis; adenoma of thyroid gland          | 59 F                  | 4/ 5 to 12  | 123 to 133                 | 40                    | 54          | 1175 to 1220      | 775 to 810     | 1.2                             |
| 4*   | Rheumatic mitral endocarditis<br>with stenosis; subacute ar-<br>thritis | 39 F                  | 4/18 to 20  | 243                        | 40                    | 92          | 2000              | 835            | 1.3                             |
| 5  | Arteriosclerosis; coronary<br>sclerosis                                 | 58 M                  |             | 76 to 122                  | 25 to 39              | 35 to 54    | 720 to 1175       | 445 to 765     | 1.1                             |
| 6  | Arteriosclerosis  | 72 F                  |             | 240                        | 40                    | 97          | 2000              | 1100           | 3.4                             |
| 7  | Arteriosclerosis; essential hy-<br>pertension                           | 47 F                  |             | 85 to 133                  | 23 to 40              | 30 to 54    | 745 to 1220       | 545 to 810     | 1.1                             |
| 8  | Arteriosclerosis  | 67 M                  |             | 62 to 116                  | 36 to 38              | 41 to 54    | 840 to 1100       | 400 to 700     | 1.1                             |
| 9  | Rheumatic mitral endocarditis;<br>auricular fibrillation                | 25 M                  |             | 97 to 148                  | 32 to 40              | 57 to 80    | 1030 to 1500      | 610 to 790     | 1.2                             |
| 10   | Arteriosclerosis; hypertension  | 46 M                  |             | 87 to 133                  | 23 to 40              | 43 to 54    | 870 to 1220       | 425 to 810     | 1.0                             |
| 11   | Arteriosclerosis; severe hyper-<br>tension                              | 57 F                  |             | 76 to 148                  | 33 to 40              | 71 to 80    | 1075 to 1500      | 700 to 810     | 1.2                             |
| 12   | Arteriosclerosis; essential hy-<br>pertension; aortic stenosis          | 45 M                  | 5/26 to 6/5 | 105 to 135                 | 26 to 40              | 47 to 54    | 1050 to 1200      | 605 to 810     | 1.2                             |
|  |   |                       | 6/ 6 to 7   | 121 to 243                 | 37 to 40              | 46 to 54    | 1080 to 1200      | 650 to 810     | 1.1                             |
|  |   |                       |             |                            | 40                    | 46 to 54    | 1050 to 1220      | 690 to 810     | 1.2                             |
|  |   |                       |             |                            |                       | 92          | 2000              | 810            | 1.2                             |

\*This diet was not weighed, but was carefully estimated daily.



## METHOD OF STUDY

The diuretic effect of digitalis was studied on three healthy human subjects, and on twelve patients with congestive heart failure and considerable edema. One patient was observed and treated on two different occasions. None of the patients exhibited evidence of serious impairment of renal function. The study was made on one of the healthy human subjects three times, varying the diet and doses of digitalis with each experiment. To insure standard experimental conditions, all the subjects were given a diet of weighed food, as constant as possible from day to day, of known low salt, water and protein content, the same as that employed by Keith, Smith and Whelan.<sup>16</sup> The weighed food both of the healthy subjects and of those with myocardial failure is shown in Table I. The total caloric values of the diet given to normal, healthy subjects were adequate, but the food given to patients with cardiac failure was low in total calories. This food was given to the patients with cardiac failure because they were at constant rest in bed, which reduced their caloric requirements, and because it was essential that all food should be eaten. The content of sodium chloride was low in all of the diets with two exceptions, and varied between 1 and 1.5 gm. daily. The diets of patient 4 and healthy subject 1, experiment 2, contained approximately twice the amount of sodium chloride that was present in the others. Attention is also called to the low water content of all the diets except that of healthy subject 1, experiment 2, and that of patient 4, which contained approximately 300 c.c. of water in excess of the others. The importance of the diet of weighed food, which was kept as constant as possible, is emphasized because there have been relatively few standardized experimental studies of digitalis in which such a diet has been employed. It is obvious that a study in which this factor is as carefully controlled as possible is of more significance and is more dependable than one in which this factor is ignored. Daily estimations were made of body weight, pulse rate, blood pressure and total output of urine in twenty-four hours. The intake of extra fluid was as constant as possible with each subject, and was carefully estimated, varying from 800 to 1,000 c.c. daily with the different subjects. A preliminary period of absolute bodily rest, with no medication other than the necessary sedatives, was given the patients who had congestive failure; the healthy subjects also had a preliminary period of control without medication. At the conclusion of the periods of control a standardized preparation of powdered leaf of digitalis was given to each subject in adequate amount.\* Electrocardiograms were taken daily of healthy subjects, and every three to four days in the cases of heart failure. Careful observation was made of all the subjects for clinical objective

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\*Burroughs Wellcome tablets containing the powdered leaf were used.

and subjective signs of digitalis effect. The output of urine for twenty-four hours was submitted daily to estimation of the total chloride, the total fixed base, and the total nitrogen content.\*

#### RESULTS IN HEALTHY HUMAN SUBJECTS

Fig. 1 shows graphically the digitalis effect in a healthy human being (subject 1) using adequate doses of digitalis in three different experiments. The daily intake of extra fluid was constant for each experiment, and was 800 c.c. in the first two experiments and 1,000 c.c. in the third experiment. The weighed diet contained 60 gm. of

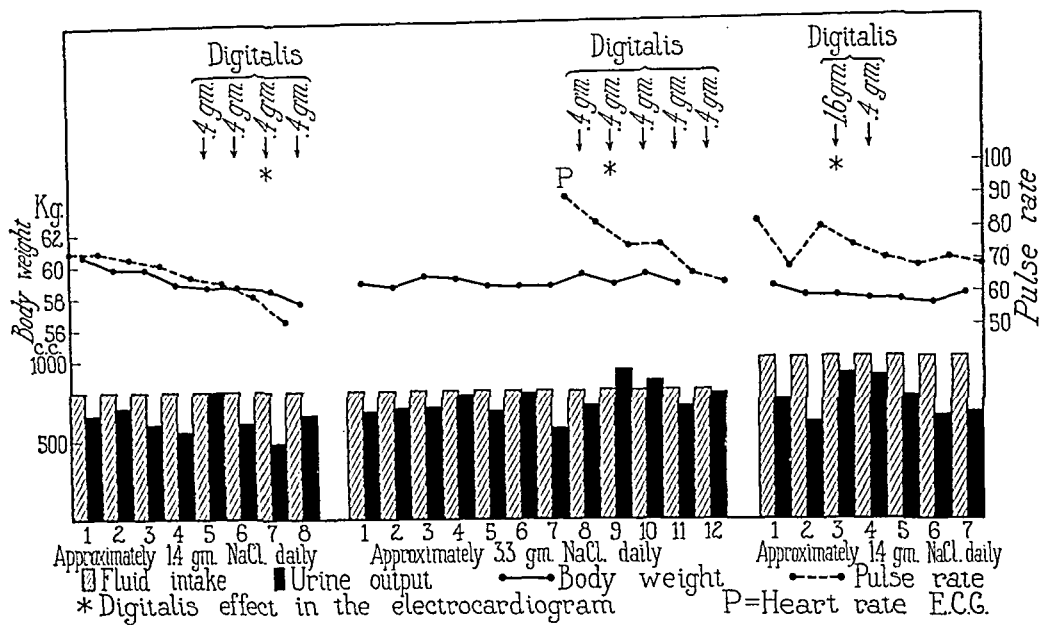


Fig. 1.—Digitalis effect on normal subject in three experiments. The effect varies when the amount of water and salt of the diet is varied. Intake of fluid does not include fluid in food.

protein, 1,500 to 2,000 calories, and was low in water and salt. The daily content of water of this diet was 820 c.c. in the first experiment, 860 c.c. in the third experiment, and 1,150 to 1,180 c.c. in the second experiment. The salt content of the diet during the second experiment, as is shown in Table I, was approximately twice that of the first and third experiments; the dietary fluid content in the second experiment was approximately 300 c.c. more than that of the first and third experiments.

Characteristic electrocardiographic evidence of digitalis effect was observed in all three of the experiments on this subject as well as on one of the other subjects (subject 2). The evidence consisted of a change in the T-wave, a prolongation of the conduction time, or both.

There was only slight diuresis in the first experiment; the output of urine rose to 800 c.c. on the first day after administration of digitalis

\*The chloride in the urine was determined by the method of Wilson and Ball. The determination of the total fixed base was by the method of Stadie and Ross. The total nitrogen was determined by the standard method of Kjeldahl.

TABLE II  
CHEMICAL STUDIES OF SUBJECT 1, EXPERIMENT 3

| FEBRUARY,<br>1931 | WT.,<br>KG.† | URINE           |                     |     |  |  |  |  |  |      |                                    | DIGITALIS<br>GM. | BLOOD*   |  |     | PLASMA<br>CHLORIDE,<br>MG. IN EACH<br>100 C.C. |
|-------------------|--------------|-----------------|---------------------|-----|--|--|--|--|--|------|------------------------------------|------------------|--|--|-----|--|
|                   |              | VOLUME,<br>C.C. | SPECIFIC<br>GRAVITY | PH  | SODIUM<br>CHLORIDE,<br>GM.             |  | FIXED BASE<br>C.C. TENTH<br>NORMAL     |  | TOTAL<br>NITROGEN, GM.                 |      | UREA<br>MG. IN<br>EACH<br>100 C.C. |                  | PLASMA<br>CARBON<br>DIOXIDE<br>COMBINING<br>POWER, PER<br>CENT |  |     |  |
|                   |              |                 |                     |     | IN EACH IN ENTIRE<br>100 C.C. SPECIMEN | IN EACH IN ENTIRE<br>100 C.C. SPECIMEN | IN EACH IN ENTIRE<br>100 C.C. SPECIMEN | IN EACH IN ENTIRE<br>100 C.C. SPECIMEN | IN EACH IN ENTIRE<br>100 C.C. SPECIMEN |      |                                    |                  |  |  |     |  |
|                   |              |                 |                     |     |  |  |  |  |  |      |                                    |                  |  |  |     |  |
|                   |              |                 |                     |     |  |  |  |  |  |      |                                    |                  |  |  |     |  |
| 19 to 20          | 58.3         | 660             | 1.015               | 5.4 | 0.24                                   | 1.58                                   | 94                                     | 620                                    | 0.87                                   | 5.74 |                                    |                  |  |  |     |  |
| 20 to 21          | 58.3         | 740             | 1.009               | 7.0 | 0.12                                   | 0.89                                   | 74                                     | 548                                    | 0.48                                   | 3.55 |                                    |                  |  |  | 617 |  |
| 21 to 22          | 57.7         | 630             | 1.023               | 5.6 | 0.25                                   | 1.58                                   | 151                                    | 951                                    | 1.34                                   | 8.44 | 34                                 | 65               |  |  |     |  |
| 22 to 23          | 57.5         | 900             | 1.016               | 5.8 | 0.21                                   | 1.89                                   | 99                                     | 891                                    | 0.92                                   | 8.28 | 34                                 | 63               |  |  | 583 |  |
| 23 to 24†         | 57.5         | 850             | 1.013               | 6.0 | 0.21                                   | 1.79                                   | 88                                     | 748                                    | 0.53                                   | 4.51 | 28                                 | 64               |  |  | 608 |  |
| 24 to 25          | 57.3         | 740             | 1.013               | 5.8 | 0.15                                   | 1.11                                   | 77                                     | 570                                    | 0.63                                   | 4.66 |                                    |                  |  |  |     |  |
| 25 to 26          | 57.7         | 650             | 1.015               | 6.8 | 0.19                                   | 1.24                                   | 116                                    | 754                                    | 0.60                                   | 3.90 | 38                                 | 62               |  |  | 581 |  |
| 26 to 27          | 57.7         | 670             | 1.012               | 7.0 | 0.11                                   | 0.74                                   | 85                                     | 569                                    | 0.49                                   | 3.28 | 40                                 | 64               |  |  | 561 |  |
| 27 to 28          | 58.0         | 720             | 1.007               | 7.2 | 0.07                                   | 0.50                                   | 68                                     | 490                                    | 0.38                                   | 2.74 |                                    |                  |  |  |     |  |

\*Blood withdrawn at 8 A.M. at end of twenty-four hours.

†Weighed at 8 A.M. at end of period of twenty-four hours.

‡Protein, 43 gm.; 1110 calories; water, 685 c.c.; approximately 1 gm. sodium chloride; extra water, 1000 c.c.

§February 22, digitalis, 0.4 gm, at 8 A.M., 2 P.M., 8 P.M.; February 23, digitalis 0.4 gm. at 2 A.M., 0.2 gm. at 8 A.M. and 2 P.M.

and thereafter quickly dropped to a level generally below that of the control period. This result indicates that the diuretic effect was negligible. However, in the second experiment is slight but definite evidence of diuresis beginning on the second day of administration of digitalis. The slight but definite increase of the amount of sodium chloride and water in the diet might be a possible factor. In the third experiment, also, there was slight diuresis for two days after administration of digitalis. The rapid method of digitalization of Eggleston was employed during this experiment. Attention is directed to the daily intake of extra fluid, amounting to 1,000 c.c. during this experiment. This was 200 c.c. more than that during the first or second experiment. The daily output of urine during the third experiment never equalled or exceeded the daily intake of extra fluid.

The results of chemical studies of the healthy human subject in experiment 3 are shown in Table II. The output of urine for twenty-four hours was examined for its content of sodium chloride, total base, and total nitrogen; the whole blood for urea, and the blood plasma for carbon dioxide combining power and chloride. There was no increase in the daily concentration of chloride of the urine after administration of digitalis in this experiment. Similar studies, in experiment 1, also failed to give evidence of increase of the concentration of chloride after ingestion of adequate doses of digitalis. There was, however, a slight increase of the concentration of chloride in the urine in the second experiment, following the use of digitalis. Attention is again directed to the fact that the intake of chloride was greater in experiment 2. Excretion of nitrogen during the first few days (Table II) was somewhat irregular, but it averaged about 5 gm. daily. On the first day, after digitalis had been taken, there was a marked in-

TABLE III  
DIURETIC EFFECT OF DIGITALIS ON SUBJECT 2

| JULY, 1930     | WEIGHT,<br>KG. * | URINE           |     |                            |                       |                           |                       |                                     |                       | DIGITALIS,<br>GM. |
|----------------|------------------|-----------------|-----|----------------------------|-----------------------|---------------------------|-----------------------|-------------------------------------|-----------------------|-------------------|
|                |                  | VOLUME,<br>C.C. | PH  | SODIUM<br>CHLORIDE,<br>GM. |                       | TOTAL<br>NITROGEN,<br>GM. |                       | FIXED BASE,<br>C.C. TENTH<br>NORMAL |                       |                   |
|                |                  |                 |     | IN EACH<br>100 C.C.        | IN ENTIRE<br>SPECIMEN | IN EACH<br>100 C.C.       | IN ENTIRE<br>SPECIMEN | IN EACH<br>100 C.C.                 | IN ENTIRE<br>SPECIMEN |                   |
| 28 to 29       | 58.8             | 550             | 5.6 | 0.52                       | 2.86                  | 1.29                      | 7.10                  | 166                                 | 913                   |                   |
| 29 to 30       | 58.3             | 450             | 5.6 | 0.49                       | 2.20                  | 1.58                      | 7.10                  | 183                                 | 823                   |                   |
| 30 to 31       | 58.3             | 500             | 5.8 | 0.29                       | 1.45                  | 1.77                      | 8.85                  | 157                                 | 785                   |                   |
| 31 to August 1 | 57.6             | 400             | 6.0 | 0.24                       | 0.96                  | 2.07                      | 8.30                  | 176                                 | 705                   |                   |
| 1 to 2         | 56.3             | 500             | 5.6 | 0.26                       | 1.30                  | 1.68                      | 8.40                  | 167                                 | 835                   | 0.4†              |
| 2 to 3         | 54.4             | 440             | 5.6 | 0.29                       | 1.27                  | 1.86                      | 8.18                  | 165                                 | 725                   | 0.4†              |
| 3 to 4         | 53.7             | 500             | 5.6 | 0.32                       | 1.60                  | 1.63                      | 8.15                  | 161                                 | 805                   | 0.4†              |
| 4 to 5         | 52.6             | 475             | 5.6 | 0.26                       | 1.23                  | 2.30                      | 10.92                 | 154                                 | 732                   | 0.4†              |

\*Weighed at 100° C.

\*Weighed at end of twenty-four hours.

†Digitalis, 0.4 gm., ingested once daily at 8:30 A.M.

crease in excretion of nitrogen, but a decrease in the next two days. Excretion of nitrogen during the last three control days after administration of digitalis was fairly constant, and averaged about 3 gm. daily.

Fig. 2 represents the digitalis effect in healthy human subject 2, who was likewise studied under carefully standardized conditions. Again, digitalis had no diuretic effect. Chemical studies of the same healthy person (subject 2) before and after administration of digitalis are shown in Table III. The concentration of chloride in the urine was not distinctly increased after the use of digitalis. Excretion of nitrogen during the first few days averaged 7.84 gm. daily. While the

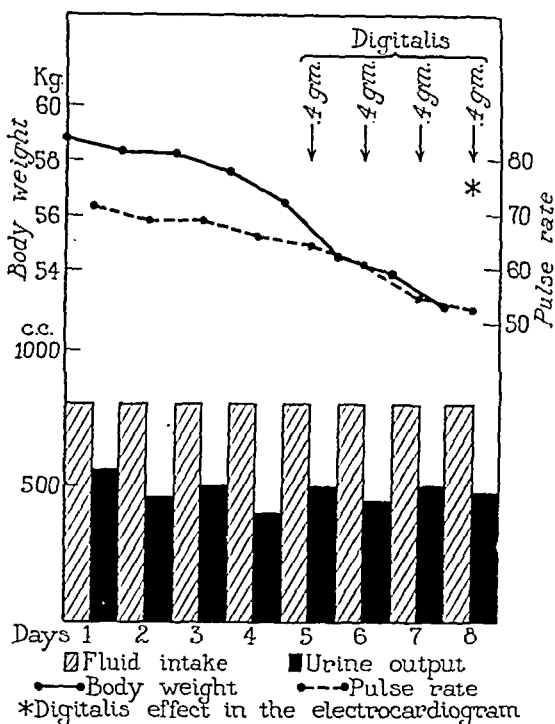


Fig. 2.—Effect of digitalis on normal subject 2. The intake of fluid does not include fluid in food.

subject was taking digitalis, excretion of nitrogen was constant for the first three days and was about the same in quantity as during the control period, averaging 8.24 gm. daily. There was an increase of excretion of nitrogen, however, on the fourth day of administration of digitalis; the total excretion on this day was 10.92 gm. The total excretion of fixed base gradually diminished daily during the control period of four days, and averaged 806 c.c. of tenth normal base daily. During and following administration of digitalis, excretion of total fixed base but was little changed, averaging 774 c.c. tenth normal base daily. Healthy human subject 3 gave evidence of no diuretic effect following adequate doses of digitalis.

Table IV contains a brief outline of the digitalis effect in all of the experiments on the healthy human subjects. Definite slowing of the

TABLE IV  
SUMMARY OF ACTION OF DIGITALIS ON HEALTHY SUBJECTS

| SUBJECT          | CONTROL PERIOD              |   |                        |  |                   |  | PERIOD OF DIGITALIS EFFECT |                              |   |                        |  |                   |                    |               |               |                     |
|------------------|-----------------------------|---|------------------------|--|-------------------|--|----------------------------|------------------------------|---|------------------------|--|-------------------|--------------------|---------------|---------------|---------------------|
|                  | PULSE, BEATS<br>EACH MINUTE | AVERAGE DAILY<br>OUTPUT OF URINE,<br>G.C. | LOSS OF WEIGHT,<br>KG. | SODIUM CHLORIDE<br>IN URINE, GM. IN<br>EACH 100 G.C. | ELECTROCARDIOGRAM |  |                            | PULSE, BEATS<br>EACH MINUTE* | AVERAGE DAILY<br>OUTPUT OF URINE,<br>G.C. | LOSS OF WEIGHT,<br>KG. | SODIUM CHLORIDE<br>IN URINE, GM. IN<br>EACH 100 G.C. | ELECTROCARDIOGRAM |                    |               |               | DIGITALIS,<br>GM.   |
|                  |                             |   |                        |  | CARDIAC<br>RATE   | RHYTHM   | T-WAVE<br>(LEAD III)       |                              |   |                        |  | RHYTHM            | T-WAVE             |               |               |                     |
|                  |                             |   |                        |  |                   |  |                            |                              |   |                        |  |                   | LEAD II            | LEAD III      |               |                     |
| 1 (experiment 1) | 74                          | 625                                       | 1.9                    | 0.22   | 86                | Sinus regular  | In-<br>verted              | 53                           | 635                                       | 1.1                    | 0.10   | 56                | Sinus<br>irregular | Dipha-<br>sic | In-<br>verted | 1.6 in four<br>days |
| 1 (experiment 2) |                             | 700                                       | 0.3                    | 0.47   | 90                | Sinus regular  | In-<br>verted              |                              | 790                                       | 0                      | 0.63   | 56 to<br>72       | Sinus<br>irregular | In-<br>verted | In-<br>verted | 2.0 in five<br>days |
| 1 (experiment 3) | 88                          | 677                                       | 0.6                    | 0.20   | 93                | Sinus regular  | In-<br>verted              | 68                           | 755                                       | 0                      | 0.15   | 68                | Sinus<br>regular   | In-<br>verted | In-<br>verted | 2.0 in 48<br>hours  |
| 2 (experiment 4) | 71                          | 475                                       | 0.9                    | 0.39   | 60                | Sinus regular  | ?                          | 58                           | 478                                       | 3.7                    | 0.28   | 51                | Sinus<br>irregular | ?             | In-<br>verted | 1.6 in four<br>days |
| 3 (experiment 5) | 66                          | 637                                       | 0                      | 0.12   | 72                | Sinus ir-<br>regular;<br>ventricular<br>premature<br>contraction | ?                          | 58                           | 562                                       | 0.9                    | 0.09   | 67                | Sinus<br>irregular | ?             | Un-<br>known  | 1.6 in four<br>days |

\*Pulse rate taken when patient was under basal metabolic conditions at 7:30 A.M.

cardiac rate was noted in all following administration of digitalis. Characteristic electrocardiographic evidence of digitalis effect was also observed in four of the five experiments. The blood pressure remained normal throughout. The diuretic effect of digitalis was negligible in the first experiment (subject 1), definite in the second experiment (subject 1), slight for two days in the third experiment (subject 1), absent in the fourth experiment (subject 2) and also absent in the fifth experiment (subject 3). Thus of the five experiments the diuretic effect was absent in three, was slight in one, and was definite in only one. The average concentration of sodium chloride in the urine was increased in one experiment after ingestion of digitalis, and was not increased in any of the remaining four experiments.

TABLE V  
ACTION OF DIGITALIS IN MYOCARDIAL FAILURE WITH DIURESIS (PATIENT 4)

| JUNE,<br>1930 | WEIGHT,<br>KG. | PULSE,<br>BEATS EACH<br>MINUTE | URINE<br>VOLUME<br>C.C. | SODIUM CHLORIDE            |                              | DIGITALIS,<br>GM. |
|---------------|----------------|--------------------------------|-------------------------|----------------------------|------------------------------|-------------------|
|               |                |                                |                         | GM. IN<br>EACH 100<br>C.C. | GM. IN<br>ENTIRE<br>SPECIMEN |                   |
| 8             | 62.3           | 90                             | 1000                    | 0.43                       | 4.30                         |                   |
| 9             | 62.3           | 88                             | 825                     | 0.48                       | 4.00                         |                   |
| 10            | 61.6           | 88                             | 700                     | 0.49                       | 3.40                         |                   |
| 11            | 61.1           | 80                             | 800                     | 0.52                       | 4.10                         |                   |
| 12            | 61.4           | 82                             | 600                     | 0.48                       | 2.90                         |                   |
| 13            | 61.1           | 86                             | 600                     | 0.45                       | 2.70                         | 0.3               |
| 14            | 61.4           | 86                             | 500                     | 0.16                       | 0.80                         | 0.2               |
| 15            | 60.5           | 68                             | 850                     | 0.16                       | 1.40                         | 0.3               |
| 16            | 60.7           | 64                             | 1025                    | 0.36                       | 3.70                         | 0.3               |
| 17            | 60.8           | 74                             | 1375                    | 0.36                       | 4.95                         | 0.3               |
| 18            | 61.0           | 80                             | 950                     | 0.31                       | 2.95                         | 0.3               |
| 19            | 59.5           | 76                             | 1150                    | 0.31                       | 3.56                         |                   |
| 20            | 59.5           | 74                             | 525                     | 0.22                       | 1.16                         |                   |
| 21            | 60.0           | 86                             | 500                     | 0.21                       | 1.05                         |                   |
| 22            | 58.3           | 84                             | 650                     | 0.18                       | 1.17                         |                   |

#### RESULTS IN CASES OF CARDIAC FAILURE AND DEPENDENT EDEMA

In all of the twelve cases of cardiac failure there was definite dependent edema in addition to the other usual signs of failure of the circulation. None of the patients exhibited evidence of serious impairment of renal function; none had a positive Wassermann reaction. In one case only there was fibrillation of the auricles. Two patients had coronary sclerosis; three had rheumatic endocarditis, and several, arteriosclerotic and hypertensive myocardial disease. Before the present study, five patients had not experienced any previous break in compensation; five had had one previous break in compensation; one patient had had two previous periods of decompensation, and one had had three periods of decompensation.

All the patients had a preliminary period of bodily rest, without medication other than the necessary sedatives. This preliminary period of rest was often of longer duration than the figures show,

owing to the fact that the charted days were only those when the patient was receiving a constant diet of weighed food. Some of the preliminary days, when the patient received salt-free, unweighed food are not shown.

Patient 4 experienced definite and sustained diuresis, beginning on the third day of administration of digitalis. The diuresis was accompanied by definite decrease in pulse rate, definite loss of weight, and marked improvement in clinical symptoms. Table V is a brief recapitulation of this case. While the diuretic response was satisfactory, the daily average output was only slightly increased over the control period (Table VIII). Despite definite diuresis, the concentration of chloride in each 100 c.c. of urine is not increased, indicating that when

TABLE VI  
ACTION OF DIGITALIS IN MYOCARDIAL FAILURE WITH SLIGHT DIURESIS (PATIENT 8)

| JULY,<br>1931 | WEIGHT,<br>KG. | PULSE,<br>BEATS<br>EACH<br>MINUTE | VOLUME,<br>C.C. | SODIUM CHLORIDE            |                              | URINE             |                             |
|---------------|----------------|-----------------------------------|-----------------|----------------------------|------------------------------|-------------------|-----------------------------|
|               |                |                                   |                 | GM. IN<br>EACH<br>100 C.C. | GM. IN<br>ENTIRE<br>SPECIMEN | DIGITALIS,<br>GM. | AMMONIUM<br>NITRATE,<br>GM. |
| 8             | 69.0           | 88                                | 400             | 0.08                       | 0.32                         |                   |                             |
| 9             | 68.4           | 80                                | 650             | 0.03                       | 0.20                         |                   |                             |
| 10            | 68.0           | 80                                | 500             | 0.04                       | 0.20                         |                   |                             |
| 11            | 67.0           | 82                                | 600             | 0.05                       | 0.30                         | 0.4               |                             |
| 12            | 67.0           | 78                                | 450             | 0.06                       | 0.27                         | 0.4               |                             |
| 13            | 68.0           | 74                                | 425             | 0.09                       | 0.38                         | 0.4               |                             |
| 14            | 67.5           | 70                                | 925             | 0.22                       | 2.04                         | 0.4               |                             |
| 15            | 67.3           | 68                                | 900             |                            |                              | 0.4               |                             |
| 16            | 67.3           | 70                                | 600             | 0.28                       | 1.68                         |                   |                             |
| 17            | 67.3           | 69                                | 550             | 0.67                       | 3.68                         |                   |                             |
| 18            | 68.0           | 69                                | 1000            | 0.30                       | 3.00                         |                   | 6                           |
| 19            | 67.0           | 72                                | 500             | 0.58                       | 2.90                         |                   | S                           |
| 20            | 66.4           | 82                                | 750             | 0.44                       | 3.30                         |                   | S                           |
| 21            | 66.4           | 100                               | 2800            | 0.75                       | 21.00                        |                   | S+                          |
| 22            | 64.5           | 100                               | 500             | 0.17                       | 0.85                         |                   | S                           |
| 23            | 65.2           | 84                                | 550             | 0.09                       | 0.50                         |                   | S                           |

+2 c.c. salyrgan given.

digitalis does cause diuresis, the diuresis resembles that which is obtained by water or urea rather than the chloride diuresis which occurs after ingestion of several diuretics, particularly certain acid-producing salts, caffeine and mercury.

Table VI represents the effect of digitalis in another of the cases of heart failure (patient 8). There was an increased output of urine beginning on the fourth day of administration of digitalis and continuing through the fifth day. Following this, however, the output of urine rapidly diminished. After a rest period of two days, administration of ammonium nitrate was started. The immediate diuretic effect of this acid-producing salt is apparent, and it is to be noted that the diuresis obtained by means of the combined use of ammonium nitrate and salyrgan (mersalyl) far excels the diuresis obtained by the use of digitalis. There was an increase in the concentration of chloride and



TABLE VII  
EFFECT OF DIGITALIS AND OTHER DIURETICS IN MYOCARDIAL FAILURE (PATIENT 7)

| OCTOBER,<br>1930 | WEIGHT,<br>KG.† | URINE           |                     |                              |                       |                              |                       | MEDICATION                   |                       |                   |
|------------------|-----------------|-----------------|---------------------|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|-------------------|
|                  |                 | VOLUME,<br>C.C. | SPECIFIC<br>GRAVITY | SODIUM CHLORIDE,<br>GM.      |                       | FIXED BASE, C.C.             |                       | TOTAL NITROGEN,<br>GM.       |                       | DIGITALIS,<br>GM. |
|                  |                 |                 |                     | IN EACH<br>100 C.C. SPECIMEN | IN ENTIRE<br>SPECIMEN | IN EACH<br>100 C.C. SPECIMEN | IN ENTIRE<br>SPECIMEN | IN EACH<br>100 C.C. SPECIMEN | IN ENTIRE<br>SPECIMEN |                   |
| 11 to 12         | 91.1            | 240             | 1.038               | 0.11                         | 0.26                  | 42                           | 101                   | 1.58                         | 3.79                  |                   |
| 12 to 13         | 91.4            | 210             | 1.033               | 0.09                         | 0.19                  | 55                           | 115                   | 1.59                         | 3.35                  |                   |
| 13 to 14         | 90.9            | 850             | 1.014               | 0.11                         | 0.93                  | 55                           | 467                   | 0.74                         | 6.29                  |                   |
| 14 to 15         | 90.9            | 750             | 1.016               | 0.10                         | 0.75                  | 52                           | 390                   | 0.77                         | 5.77                  |                   |
| 15 to 16         | 91.2            | 730             | 1.015               | 0.12                         | 0.88                  | 67                           | 490                   | 0.70                         | 5.11                  |                   |
| 16 to 17         | 90.9            | 670             | 1.020               | 0.14                         | 0.94                  | 99                           | 663                   | 0.72                         | 4.82                  | 0.4               |
| 17 to 18         | 90.4            | 1050            | 1.016               | 0.19                         | 2.00                  | 97                           | 1018                  | 0.57                         | 5.99                  | 0.4               |
| 18 to 19         | 90.2            | 950             | 1.017               | 0.39                         | 3.70                  | 134                          | 1273                  | 0.52                         | 4.94                  | 0.4               |
| 19 to 20         | 89.5            | 700             | 1.018               | 0.43                         | 3.01                  | 142                          | 994                   | 0.59                         | 4.13                  | 0.4               |
| 20 to 21         | 89.2            | 900             | 1.017               | 0.36                         | 3.24                  | 118                          | 1062                  | 0.58                         | 5.22                  | 0.4               |
| 21 to 22         | 89.1            | 500             | 1.018               | 0.25                         | 1.25                  | 100                          | 500                   | 0.72                         | 3.60                  |                   |
| 22 to 23         | 89.0            | 550             | 1.019               | 0.25                         | 1.38                  | 97                           | 533                   | 0.78                         | 4.30                  |                   |
| 23 to 24         | 88.9            | †               |                     |                              |                       |                              |                       |                              |                       |                   |
| 24 to 25         | 89.1            | †               |                     |                              |                       |                              |                       |                              |                       | 8.0               |
| 25 to 26         | 88.6            | 360             | 1.022               | 0.14                         | 0.50                  | 122                          | 439                   | 0.69                         | 2.48                  | 8.0               |
| 26 to 27         | 86.8            | 2050            | 1.009               | 0.61                         | 12.50                 | 138                          | 2329                  | 0.12                         | 2.46                  | 8.0               |
| 27 to 28         | 86.7            | 250             | 1.020               | 0.11                         | 0.27                  | 116                          | 290                   | 0.77                         | 1.93                  | 8.0               |
| 28 to 29         | 86.4            | 380             | 1.026               | 0.14                         | 0.53                  | 108                          | 410                   | 1.00                         | 3.80                  | 8.0               |
| 29 to 30         | 86.1            | 600             | 1.020               | 0.44                         | 2.64                  | 154                          | 924                   | 0.72                         | 4.32                  | 6.0               |
| 30 to 31         | 83.9            | 2660            | 1.011               | 0.68                         | 18.09                 | 143                          | 3804                  | 0.13                         | 3.46                  | 8.0               |
| 31 to November   | 83.9            | 550             | 1.017               | 0.23                         | 1.27                  | 112                          | 616                   | 0.30                         | 1.65                  | 8.0               |
| 1 to 2           | 83.4            | 550             | 1.021               | 0.10                         | 0.55                  | 115                          | 632                   | 1.00                         | 5.50                  | 8.0               |

\*Digitalis 0.1 gm. 8 A.M., 12 M., 4 P.M., and 8 P.M.; ammonium nitrate 2 gm. at 8 A.M., 12 M., 4 P.M., 8 P.M.; salyrgan given intravenously.

†Weighed at end of twenty-four hours.

‡Not accurately collected.

in the total excretion of chloride in the urine on the fourth day of administration of digitalis, but this was not nearly so much as that obtained by the use of ammonium nitrate and salyrgan.

The digitalis effect in another of the cases of cardiac failure (patient 7) may be seen in Table VII. This patient had arteriosclerosis, essential hypertension, obesity, and myocardial degeneration with marked cardiac failure. Together with the other usual signs of failure of the circulation, there was marked generalized edema and ascites. After a preliminary period of rest, digitalis was administered in adequate amounts over a period of five days. Definite diuresis was noted the second and third days of administration of digitalis. There was likewise some diuresis on the fifth day of administration of digitalis. Following this, the output of urine diminished and was below that of the control period. After an interval period of five days of rest, the patient was given ammonium nitrate and salyrgan. The superior diuretic properties of the latter drugs in comparison with digitalis are apparent. The average total daily output of urine during the control period was 556 c.c. During the period of five days of administration of digitalis, and the next two days, the average total daily output of urine was 760 c.c., whereas the average for the period of administration of ammonium nitrate and salyrgan was 925 c.c. The patient eventually became completely free of edema by the combined use of ammonium nitrate and salyrgan. The concentration of chloride in each 100 c.c. of urine was increased by the administration of digitalis but did not reach so high a concentration as with the use of ammonium nitrate and salyrgan. The total excretion of sodium chloride in the urine was much greater with the combined use of the latter diuretics than with administration of digitalis. Excretion of fixed base was likewise increased with administration of digitalis, but there was also a more marked increase of excretion of fixed base with the combined use of ammonium nitrate and salyrgan than with digitalis. The excretion of total nitrogen in the urine was changed little, if at all, by use of digitalis, and was definitely diminished during the administration of ammonium nitrate and salyrgan.

A brief summary of the results of digitalis effect in the twelve cases of heart failure is shown in Table VIII.

In studying the diuretic effect of digitalis, patients whose total daily output of urine was 1,000 c.c. or more were classified as showing definite diuresis; those whose output of urine varied from 700 to 780 c.c. were classified as having obtained slight diuresis, and those whose total daily output of urine was less than 700 c.c. were classified as having obtained no diuresis. By this division of the patients, three obtained definite diuresis after administration of digitalis; in four, diuresis was slight, and five failed to obtain any diuretic effect despite adequate therapeutic administration of digitalis. Four patients became com-

TABLE VIII  
SUMMARY OF ACTION OF DIGITALIS IN MYOCARDIAL FAILURE

| PATIENT                   | EDEMA,<br>GRADE | REST PERIOD                                     |                                   |   |  |                              |               | DIGITALIS EFFECT                                |                                   |   |   |               |                              |
|---------------------------|-----------------|---|-----------------------------------|---|--|------------------------------|---------------|---|-----------------------------------|---|---|---------------|------------------------------|
|                           |                 | ELECTRO-<br>CARDIO-<br>GRAM,<br>CARDIAC<br>RATE | PULSE<br>BEATS<br>EACH<br>MINUTE* | AVERAGE<br>DAILY<br>OUTPUT<br>OF URINE,<br>C.C. | AVERAGE<br>AMOUNT OF<br>CHLORIDE IN<br>URINE, GM.<br>IN EACH<br>100 C.C. | LOSS<br>OF<br>WEIGHT,<br>KG. | EDEMA<br>FREE | ELECTRO-<br>CARDIO-<br>GRAM,<br>CARDIAC<br>RATE | PULSE<br>BEATS<br>EACH<br>MINUTE† | AVERAGE<br>DAILY<br>OUTPUT<br>OF URINE,<br>C.C. | AVERAGE<br>AMOUNT OF<br>CHLORIDE<br>IN URINE,<br>GM. IN<br>EACH 100<br>C.C. | DI-<br>URESIS | LOSS<br>OF<br>WEIGHT,<br>KG. |
| 1 (first ad-<br>mission)  | 2               | 90  | 80                                | 750   | 0.74   | 0                            | Yes           | 60  | 68                                | 1665  | 0.45  | Yes           | 12.0                         |
| 1 (second ad-<br>mission) | 1               | 75  | 76                                | 1395  | 0.32   | 2.5                          | Yes           |   | 42                                | 1100  | 0.20  | Yes           | 1.4                          |
| 2                         | 3               | 100   | 100                               | 800   | 0.39   | 0.3                          | Yes           | 70  | 76                                | 1115  | 0.53  | Yes           | 8.3                          |
| 3                         | 2               | 99  | 80 to 105                         | 510   | 0.16   | 0                            | Yes           |   | 84 to 110                         | 1030  | 0.38  | Yes           | 9.5                          |
| 4                         | 1               | 96  | 82                                | 785   | 0.48   | 0.9                          | No            | 78  | 76                                | 795   | 0.27  | +             | 2.4                          |
| 5                         | 3               | 90  | 80                                | 790   | 0.78   | 2.4                          | No            | 71  | 70                                | 795   | 0.65  | +             | 6.1                          |
| 6                         | 2               | 60  | 60 to 70                          | 1365  | 0.47   | 3.2                          | No            |   | 60 to 70                          | 765   | 0.30  | +             | 4.0                          |
| 7                         | 3               | 80  | 70                                | 555   | 0.11   | 0                            | No            | 68  | 100                               | 715   | 0.28  | +             | 1.8                          |
| 8                         | 2               | 84  | 80                                | 515   | 0.05   | 1.0                          | No            | 71  | 70                                | 635   | 0.23  | No            | 0.7                          |
| 9                         | 3               | 79  | 80                                | 430   | 0.70   | 1.2                          | No            | 58  | 76                                | 550   | 0.51  | No            | 2.0                          |
| 10                        | 1               |   | 84                                | 845   | 0.82   | 7.6                          | Yes           | 86  | 66                                | 585   | 0.41  | No            | 3.7                          |
| 11                        | 3               | 106   | 90                                | 320   |  | 0                            | No            | 66  | 90                                | 635   |   | No            | 8.9                          |
| 12                        | 2               | 95  | 84                                | 465   | 0.11   | 3.5                          | No            |   | 84                                | 545   | 0.22  | No            | 6.3                          |

\*Pulse rate taken, 7:30 A.M. on last day of control period and at 7:30 A.M. on the day after the last dose of digitalis.

†Eight months between admission.

‡Slight amount of diuresis.

pletely free of edema following use of this drug, and the edema increased in one case. The average daily intake of extra fluid of the whole group during the time digitalis was given was 774 c.c., whereas the average total daily output of urine was 816 c.c.; the greatest output on any one day was 1,665 c.c., and the least output, 510 c.c. The pulse rate of seven of the twelve patients was slowed following the use of digitalis, varying from four to thirty-four beats to the minute, averaging thirteen beats to the minute. The pulse rate of three patients was not changed, and two patients had an increased pulse rate after administration of digitalis. In the electrocardiogram of each patient was the characteristic sign of digitalis effect described by Cohn. No appreciable change could be noted in the blood pressure in any of the cases following the use of digitalis.

Practically all of the patients showed definite symptomatic improvement following treatment with digitalis. This improvement was evidenced by lessened dyspnea, improved color, the ability to sleep, signs of improvement of the circulation, and general increase in comfort. In general the patients who obtained the best diuretic effect had the most marked clinical improvement. However, some of the patients who had no diuretic effect showed clinical evidence of beneficial digitalis effect. With or without diuresis, patients with cardiac failure may show evidence of marked benefit after the use of digitalis.

#### COMMENT

The findings in the healthy human subject, under the conditions of these experiments, indicate that digitalis in therapeutic doses exerts slight if any diuretic effect. My data suggest that sodium chloride and water in the diet may be a possible causative factor when diuresis occurs. Definite slowing of the pulse rate following administration of digitalis was observed in all of the five experiments on the three healthy human subjects; the degree of slowing varied from eight to twenty beats to the minute. This is not in agreement with the findings of Cohn. He stated that in the absence of edema reduction in the cardiac rate occurs, principally in the "hypodynamic or unstable heart or the heart which for unknown reasons undergoes spontaneous alterations in rate," and that aside from these the majority of persons do not respond to therapeutic doses of digitalis by a fall in the cardiac rate. Cushny regarded the slowing in cases of normal rhythm as entirely due to the inhibiting action of digitalis.

Despite clinical and electrocardiographic evidence of the effect of digitalis, the diuretic action of this drug was uncertain, even though all the patients had definite myocardial failure and edema. Several of the patients failed to obtain any diuresis after adequate administration of digitalis. In none of the cases was the diuresis so marked as

has been experienced with these and many other patients who have been given other diuretic substances.

In combating the edema of myocardial failure, for some time diuretic substances other than digitalis have been employed in The Mayo Clinic. Since the combined uses of digitalis and other diuretic substances in the treatment of such cases, the results have been much more encouraging.

#### SUMMARY

Digitalis, when given to the healthy human subject in therapeutic doses and under experimental conditions laid down in this study seems to exert slight, if any, diuretic effect. The diuretic effect of digitalis in cases of cardiac failure with edema is uncertain; such effect may be marked, slight, or absent. It is suggested that in the treatment of congestive heart failure and edema digitalis be employed for its beneficial cardiac effect, and that other substances be also employed for their superior and more certain diuretic action.

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# GONOCOCCUS ENDOCARDITIS\*

## REPORT OF A CASE

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NEW YORK, N. Y.

SINCE the publication in 1922 of Thayer's<sup>1</sup> comprehensive article on the cardiac complications of gonorrhea, there have appeared in the literature only 12 cases of gonococcus carditis indisputably proved by bacteriological means. In addition to these, six writers have discussed other cases either presenting strong presumptive evidence of this condition or illustrating various methods of treatment after diagnosis. It is the purpose of this paper to report a case in which an unusually detailed history was available and in which a very full post-mortem analysis was carried out; as well as to summarize the recent literature on the subject.

Thayer's series comprised 20 cases either coming under his own observation or collected from the records of Johns Hopkins Hospital, in addition to 60 from the literature. He describes endocarditis of gonococcal origin to be of an ulcerating vegetative nature, usually acute in onset, coming on at varying periods after the initial infection, and pursuing a rapid fulminating course to death in from four to nine weeks, as a rule. The fever is of the high remittent type, a marked anemia develops rapidly, embolic phenomena are usually present, and the constitutional symptoms throughout are very grave.

The age incidence given by Thayer is nine to forty-two years; that in the 13 cases, including our own, reviewed here is nine to thirty-two, the average being twenty-three years. A preponderance of males is noted in the first series; in the later cases the sexes are equally divided. The average duration of the disease is about ten weeks in both instances, though 4 cases are noted by Thayer as exceeding fourteen weeks, the upper limit of the later group. In regard to the anemia, leucocytosis, and embolic phenomena, the statistics originally presented are fully confirmed by subsequent observations. Recent data concerning the precise nature of the renal lesions found seem too indefinite to warrant an attempt at interpretation in this place. Thayer reported the existence of an acute or subacute nephritis in most of his cases, these being more striking the longer the duration of the disease. Arthritis in Thayer's literature was reported in 68.5 per cent of cases; in his own series in only 31.1 per cent; in the 13 cases reviewed here this complication was noted in 6, or 46.2 per cent.

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In only one<sup>2</sup> of these 13 cases was there an absence of definite genital gonorrhea.

In the matter of anatomical distribution of the lesions, it has seemed well to tabulate the various findings:

TABLE I

|              |       | JOHNS HOPKINS<br>HOSPITAL<br>(20 CASES) | PREVIOUS<br>LITERATURE<br>(60 CASES) | LATER<br>LITERATURE<br>INCLUDING<br>PRESENT CASE<br>(13 CASES) | TOTALS     |
|--------------|-------|---|--------------------------------------|--|------------|
| Left         | A     | 6                                       | 30                                   | 5  | 41         |
|              | M     | 12                                      | 15                                   | 3  | 20         |
|              | MA    | 12                                      | 8                                    | 2  | 22         |
|              | Aorta | 12                                      | 0                                    | 0  | 12         |
|              | Total | 12 (60%)                                | 53 (88.3%)                           | 10 (77%)   | 75 (80.7%) |
| Right        | P     | 4                                       | 1                                    | 2  | 7          |
|              | T     | 1                                       | 0                                    | 0  | 1          |
|              | PT    | 0                                       | 1                                    | 0  | 1          |
|              | Total | 5 (25%)                                 | 2 (3.3%)                             | 2 (15%)  | 9 (9.65%)  |
| Both         | AP    | 0                                       | 1                                    | 0  | 1          |
|              | AT    | 2                                       | 1                                    | 0  | 3          |
|              | MT    | 0                                       | 0                                    | 1  | 1          |
|              | APM   | 0                                       | 1                                    | 0  | 1          |
|              | APT   | 1                                       | 0                                    | 0  | 1          |
|              | AMT   | 0                                       | 1                                    | 0  | 1          |
|              | AMPT  | 0                                       | 1                                    | 0  | 1          |
|              | Total | 3 (15%)                                 | 5 (8.3%)                             | 1 (8%)   | 9 (9.65%)  |
| Pericarditis |       | 4 (20%)                                 |                                      | 3 (23%)  | 7 (7.4%)   |

A = aortic; M = mitral; MA = mitral and aortic; T = tricuspid; P = pulmonary.

Two cases in the Johns Hopkins series showed involvement of the aortic wall as well as of the aortic valve; one similar case is reported in the recent literature.

It has seemed inadvisable to record the occurrence of the acute endocarditis on previously unaffected as against chronically diseased valves, owing to uncertainty in the condensed protocols of some reported cases. Thayer has pointed out, from his observations, a predilection of the gonococcus, in common with the staphylococcus and pneumococcus, for previously uninvolved valves. It should be noted especially that right-sided involvement occurred in only 2<sup>3, 4</sup> of these 13 cases, a percentage considerably less than that observed by Thayer. In view of the anatomical proximity of the pericardium to the endocardium in the neighborhood of the aortic valve, the occurrence of pericarditis in only about one-fifth of all cases seems remarkable.

#### CASE REPORT

L. L. (Path. 16330), male, aged twenty-three years, was admitted to the urological service of Bellevue Hospital, December 16, 1930, with a chief complaint of swelling behind the scrotum. Five weeks previously he had noticed a urethral discharge,



which had continued without other complication until five days before admission, when a swelling was noted in the perineum. There had been chills and fever for three days, and the swelling had become painful and steadily larger.

*Past History.*—Patient denied any previous venereal disease. He had chorea at the age of twelve; no tonsillitis or rheumatic fever. In 1928, he noted precordial pain and dyspnea on exertion, with occasional edema of legs, and for a while he ran a temperature up to 102°. In September, 1930, he was admitted to Beekman Street Hospital complaining of stabbing precordial pain, loss of weight, and insomnia. His heart was not enlarged to percussion; the first sound at the apex was sharp and localized; the second pulmonic sound was accentuated, and there was a soft systolic murmur at the apex. Orthodiagram showed slight accentuation of the left auricular curve but no cardiac enlargement. The urine was negative. The hemoglobin was 85 per cent. The leucocyte and differential counts were normal. The Wassermann reaction was negative. There was no temperature. The patient was discharged symptom free after five days' rest in bed.

*Family History.*—Essentially negative.

*Examination.*—Local condition: Swelling over bulbous urethra; no fluctuation. Purulent urethral discharge. Prostate slightly enlarged and very soft. General: Pale, somewhat dyspneic, moderately ill-appearing. Heart: Apex impulse felt in the fifth interspace within the nipple line. No murmurs heard. Temperature: 101° F.

*Laboratory Findings.*—Leucocytes 15,500, 82 per cent polynuclears. Wassermann reaction negative. Blood nonprotein nitrogen 34 mg. Blood pressure 130/70 mm. Phenolphthalein excretion 45 per cent in two hours. Blood culture negative on ordinary agar and meat-infusion broth.

*Course.*—The perineal abscess was incised, but no pus was obtained. There was no extension of the process; the temperature came down to normal for two days. On the fourth day it rose abruptly to 104.6° F., and the patient was somewhat irrational. Attempts to catheterize were unsuccessful because of stricture of urethra. On the eighth day the patient began to sweat profusely, coughed frequently, and showed several very small petechial hemorrhages in the right conjunctiva, as well as a single one in the left. The heart was seen to be definitely enlarged; there was roughening of the first sound at the apex, and over the aortic area, transmitted to the left of the sternum and toward the apex, was heard a long diastolic, as well as a long systolic, murmur. The pulse was Corrigan in type, and capillary pulsation was noted. The lungs were negative. There was slight edema of both ankles.

A diagnosis of rheumatic heart disease was made and the patient was transferred to a medical ward. The patient looked desperately ill, but a second blood culture was also negative. Marked decompensation set in, and on the fourteenth day the spleen was felt. The temperature was spiking to 105° daily; the urine remained negative. A third blood culture was reported negative. On the twenty-second day the patient was very weak; many petechiae were seen in the conjunctivae, and a fourth blood culture was taken, which was later reported negative. The patient died on the twenty-third day after admission.

*Clinical Diagnosis.*—Rheumatic heart disease. Acute endocarditis.

*Autopsy* was performed two hours after death. *Anatomical Diagnosis.* Heart: Ulcerative vegetative bacterial endocarditis of aortic valve (*gonococcus*), sub-endocardial abscess with extension into pericardium, diffuse suppurative and hemorrhagic pericarditis, chronic productive mitral and aortic valvulitis, hypertrophy and dilatation; Kidneys: Acute intracapillary glomerular nephritis, acute focal interstitial nephritis, parenchymatous degeneration; Spleen: Infarction and suppuration (Mx); Brain: Acute suppurative leptomeningitis (Mx); Liver: Parenchyma-

tous degeneration and congestion; Stomach: Suppurative gastritis (Mx); Lungs: Congestion, bilateral hydrothorax; General: Ascites, conjunctival petechiae, gangrene of legs, decubitus ulcer, emaciation, operative perineal scar.

*Positive Gross Findings.*—Moderate emaciation. A number of small petechial hemorrhages in both conjunctivae; none in other mucous membranes or on trunk or extremities. The lower two-thirds of the right leg and the lower one-third of the left, including the feet, were the seats of a diffuse dusky cyanosis, the line of demarcation about the calves being irregular but definite. There was a superficial bed sore over the left buttock. In the perineum was a recent unhealed operative scar 4 inches in length.

*Heart.*—The precordium was markedly enlarged. On opening the pericardium about 500 c.c. of opaque brownish fluid material was found free within the sac. There were no pericardial adhesions. The pericardium itself was markedly thickened, injected, and covered with exudate, and the inner surface showed a number of hemorrhages, irregular in outline. The heart showed on its epicardial surface the same changes as noted in the pericardium. Its weight was 420 gm. The right heart was essentially natural. The left auricle was slightly dilated. The contents of the left heart were currant-jelly clot, none of which was adherent. The musculature of the left ventricle was 16 mm. in thickness, of a reddish brown color, without gross evidence of fibrosis. The mitral valve admitted one and a half fingers with ease, and showed a thickened opaque rolled-up edge on which were a row of translucent pinhead verrucae. The chordae tendineae were slightly shortened and thickened, with hypertrophy of the papillary muscles, which showed fibrosis at their tips. There was irregular vascularization of the mitral leaflet.

Attached to and replacing the left anterior cusp of the aortic valve, and extending down on the aortic leaflet of the mitral valve, was an irregular bulky friable vegetation, the total diameter of which was about 3 cm. The vegetation completely destroyed the left anterior valve cusp and ulcerated through the aortic leaflet of the mitral, appearing as an oval-shaped vegetation on the left auricle and the auricular aspect of the mitral valve leaflet. Before the heart was opened, this vegetative mass had filled the lumen of the aortic valve except for an aperture perhaps 5 mm. in diameter. The other two cusps of the aortic valve were thickened along their edges and were fused for a distance of from 1 to 2 mm. at their commissures, but showed no vegetations. The vegetation was adherent to the border of the posterior cusp, obliterating this commissure. Between the left anterior and right anterior cusp, section into the endocardium revealed a pocket between the endocardium and the outer coat of the heart at this point. This pocket contained about 5 c.c. of grayish-red purulent material which appeared the same as that found in the pericardial sac, and it was separated from the inflamed pericardium by a very thin layer of tissue. Except for the above areas, the endocardium of the left ventricle was smooth and transparent. The coronary arteries were narrow and delicate in texture, and were without sclerosis. There were a few raised yellow intimal plaques on the aorta, which for the most part was of normal diameter and elasticity. The iliac arteries were normal as far as their entrance to the thighs; beyond which examination was not permitted.

*Lungs.*—There were no noteworthy findings except congestion.

*Liver.*—The liver weighed 1880 gm., was of a red brown color, firm in consistency. Parenchyma was grossly normal except for congestion of the larger vessels. Gall bladder and bile ducts were natural.

*Spleen.*—The spleen weighed 270 gm., was of a purplish blue color, and on its surface were seen several irregularly circumscribed raised white infarcted areas. On section, these were seen to be wedge-shaped; one involved the entire upper pole of the organ and was broken down and hemorrhagic in its center. Congestion was marked. Lymphoid follicles were very prominent.

*Kidneys.*—They weighed 380 gm. together, were imbedded in normal fat and connective tissue, were a dull red brown color and somewhat flabby in consistency. On section, the cortex bulged out from a slightly retracted capsule which, however, stripped with ease, exposing a perfectly smooth mottled brown surface without evidence of hemorrhage. The cortex was swollen, and the markings were somewhat obscured. The glomeruli did not stand out prominently. Medulla, pelvis, and ureters were natural. No infarcts were noted. The larger renal vessels appeared natural.

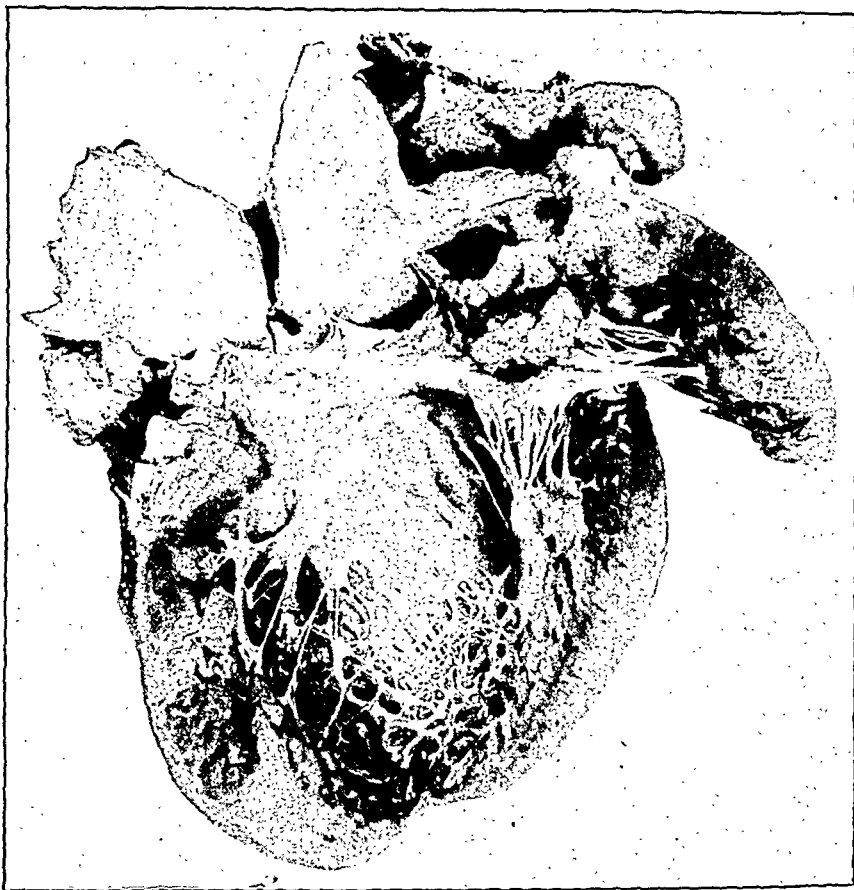


Fig. 1.—Photograph of the heart, opened to show the fungating lesion of the aortic valve.

*Bladder, Prostate, and Seminal Vesicles.*—No noteworthy changes.

*Testes.*—Appeared natural.

*Adrenals.*—Appeared natural.

*Gastrointestinal Tract and Pancreas.*—No gross abnormalities.

*Brain.*—Scalp, skull, meninges, and brain substance appeared grossly entirely natural. Section through cortex, internal capsule, and brain stem revealed no recognizable areas of softening or hemorrhage.

**MICROSCOPICAL EXAMINATION.**—*Heart.*—Sections were cut through all valves, the vegetation, the myocardium of both ventricles, and the auricles. These were first fixed in Kaiserling I, and subsequently mordanted in Zenker's fluid. Paraffin sections were stained with hematoxylin-eosin, by Giemsa's method, by Weigert's method for elastic tissue, by van Gieson's method, by the Gram-Weigert technic, and by Brown's<sup>5</sup> picric acid differential method.

The aortic valve cusp replaced and covered by vegetation in the gross was almost entirely replaced microscopically by a disintegrating necrotic mass consisting mainly

of fibrin and leucocytes, which in Giemsa-stained sections showed enormous numbers of micro-organisms in large colonies as well as discretely. The bacterial colonies were most dense around the periphery of the vegetation corresponding to the aortic valve, and about the upper margins of the sinus of Valsalva. In the center of the vegetation a few strands of necrotic valve substance could be recognized, around which the vegetation was built up. In this necrotic valve remnant no evidence of vascularization could be noted. The necrotic valve remnant was definitely made out in sections prepared with Weigert's elastic stain.

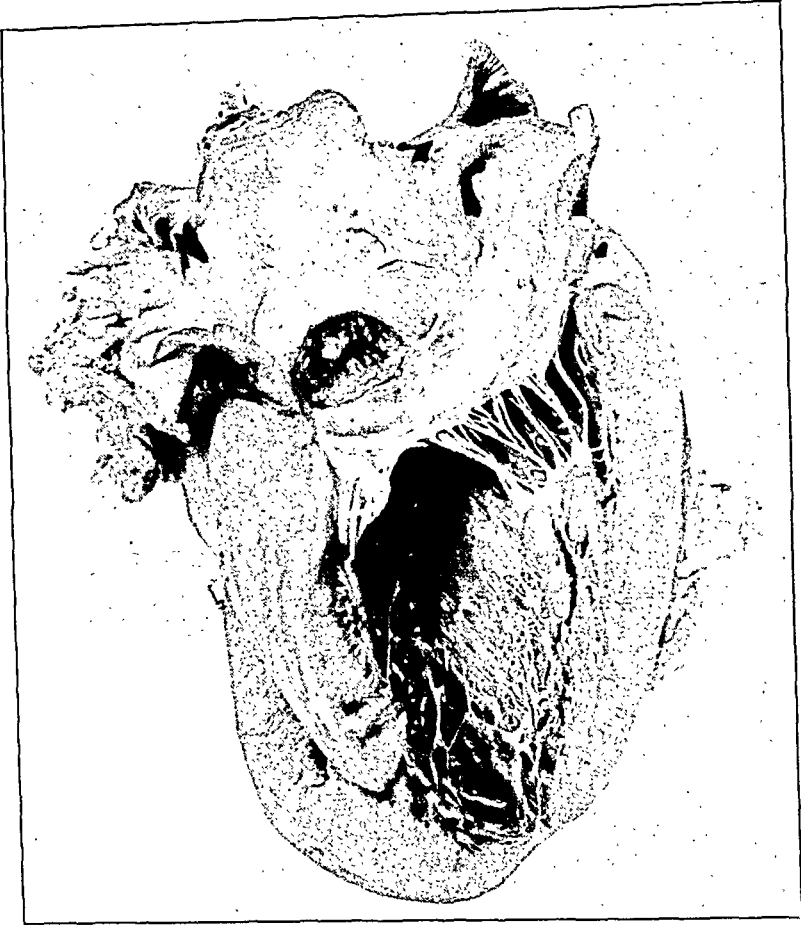


Fig. 2.—Photograph of the heart showing the auricular aspect of the mitral valve leaflet, through which the vegetation has ulcerated.

The aorta above the commissures showed slight roughening of the intima. The media was fairly intact and of normal thickness. The adventitia was markedly thickened by an infiltration of purulent and fibrinous exudate, which was continuous with the mass of necrotic fibrin and bacteria around the commissure. There was a direct extension of the suppurative process in the adventitia to the pericardium covering the aorta. The heart muscle beneath the valve, especially that posterior to it, was fragmented where it merged in an irregular serrated line with the inflammatory tissue. There was in this region considerable invasion of the muscle by leucocytes and bacteria, either isolated or in small groups, and by a growth of granulation tissue rich in fibroblasts and newly formed capillaries. This area showed also a considerable amount of nuclear detritus and degenerating muscle tissue. The base of the aortic valve showed slight fibrous thickening, this fibrous tissue showing invasion by inflammatory cells. Section through the right anterior aortic cusp showed thickening due to the presence of fibrous connective tissue. The base of the valve showed fibrous thickening and, in addition, an infiltration of round

cells, fibroblasts, and a few capillaries surrounded by polynuclear leucocytes. The valve substance was not vascularized.

The inflammatory reaction described above penetrated the septum almost to the point of origin of the tricuspid valve. This, however, was not involved, and presented no noteworthy features. The pulmonary valve showed no abnormalities. Sections through all parts of the heart showed a marked suppurative pericarditis. The pericardium was thickened owing to an overgrowth of granulation tissue rich in capillaries, round cells, plasma cells, polynuclear leucocytes, and fibroblasts which had begun to deposit collagen fibrils. The serous covering was missing, and the granulation tissue was covered by an irregular layer of fibrin. In places, small masses of hyalinized fibrous tissue were seen projecting from the surface. In a few places where the subendocardial fat was scant, the inflammatory process in the pericardium extended into the superficial layers of the myocardium.

The mitral valve showed changes of special interest. The leaflet was definitely thickened. The substance of the valve had an acellular appearance with marked overgrowth of fibrous tissue, and appeared to be entirely covered by endothelium. Strands of elastic tissue could be seen scattered throughout the valve. The cusp was definitely vascularized, the vessels extending from the base into the substance of the valve. The vessels at the valve base were compressed, but showed no intrinsic changes of note except slight thickening. There was no cellular infiltration in this area. The chordae tendineae showed fibrous thickening. In the myocardium of the left ventricle, there were a few small areas where the fibrous tissue of the intermuscular septa appeared definitely increased in amount. This fibrous tissue did not show any cellular infiltration.

The coronary arteries appeared natural throughout.

Bacteriological examination of Giemsa-stained sections revealed diplococci, cocci in short chains and small groups, and short thin bacilli. Sections stained by Brown's differential method showed numerous definite biscuit-shaped gram-negative diplococci, most of which were intracellular. In addition, other organisms were seen as noted above.

*Kidneys.*—There was a very diffuse and marked tubular degeneration, the lining epithelium being swollen and granular, with desquamation of cellular and nuclear material into the lumina. The glomerular tufts showed a fairly characteristic knotted appearance. The cellularity of the tufts appeared slightly increased. The capillary loops were visible but did not appear to contain any red blood cells, although polynuclear leucocytes were plentiful. There was some swelling of the capillary endothelium. The capsular epithelium for the most part was normal, although in an occasional glomerulus a few cells were swollen and showed proliferation. In most cases the capsular space was well preserved, but in some instances a few polynuclear leucocytes were seen within it. In the interstitium just outside the capsule of almost all the glomeruli there was a thin layer of polynuclear leucocytes. In certain afferent arterioles the endothelium was swollen and the narrowed lumina contained polynuclear leucocytes which were continuous with those in the capillary tufts.

Scattered throughout, and chiefly in conjunction with the pericapsular polynuclear infiltration, there were small focal interstitial collections of polynuclear leucocytes which in places had penetrated to the lumina of adjacent tubules. A careful search through numerous sections of kidney revealed only a single instance where a portion of a tuft appeared to be plugged by an embolus.

The renal arteries appeared natural.

*Spleen.*—There were multiple infarctions. Thrombi were in many vessels, with exudation of polynuclear leucocytes in considerable numbers into the perivascular parenchyma. The pulp spaces in areas distant from the infarcts showed numerous

polynuclear cells. The lymph follicles stood out very prominently, but were not hyperplastic. No gross bacterial colonies were made out.

*Liver.*—The liver cells appeared swollen. The Kupffer cells were prominent, their cytoplasm containing small pigment granules. The sinusoids contained polynuclear leucocytes. There was slight passive congestion.

*Stomach.*—The stroma of the mucosa showed an intense suppurative inflammation.

*Prostate and Testes.*—Essentially natural.

*Brain.*—The cortex was natural, although a few vessels showed some perivascular exudation of polynuclear leucocytes. There was marked leptomeningeal congestion, with thickening; numerous polynuclear leucocytes were seen, most of which were around the vessels.

**BACTERIOLOGICAL FINDINGS.**—As soon as the sternal plate had been removed, the pericardial sac was seared with a knife. About 20 c.c. of straw-colored cloudy fluid were removed with a sterile syringe. Part of this fluid was cultured in hormone broth and hormone agar, while the remainder was used for making smears. The smears made from the unsedimented pericardial fluid revealed numerous pus cells and gram-negative biscuit-shaped diplococci, many of which were included in the pus cells. Both the culture media revealed the same organism in pure culture in forty-eight hours. Postmortem blood cultures were also made in hormone broth medium. Gram-negative biscuit-shaped diplococci were also recovered in forty-eight hours.

On hormone agar plates, the organism grew with the characteristics usually ascribed to the gonococcus. The culture unfortunately died out before sugar tests could be performed.

#### COMMENT

The situation of the abscess at the commissure, together with the continuity, traced microscopically, of the suppurative vegetation and the inflamed pericardium at the aortic junction, explains the pericarditis; and, in view of the preponderance of aortic lesions in this condition, makes the comparative rarity of the complication noteworthy.<sup>6</sup> Interesting also is the demonstration, in Weigert-elastic-stained sections, of remnants of the aortic valve; no vascularization can be made out, and the vegetative process would seem to be laid down from without, rather than originating as an intrinsic embolism from the primary focus. Although there is no focal myocarditis of the type characterized by Aschoff's bodies, the changes in the mitral valve, with the patchy myocardial fibrosis, and also the old lesions in the aortic valve, point to the existence of a previous inflammatory process, probably rheumatic in type and having as its etiology the childhood chorea. The occurrence of the acute endocarditis on the previously involved aortic valve is relatively rare, according to Thayer.

The kidney changes are those of an early acute intracapillary and extracapsular glomerular nephritis, and of an acute focal interstitial nephritis. These renal changes must be interpreted as being on a toxic or septic rather than on an embolic basis, as the latter phenomenon was observed only in rare instances. The microscopical findings in the meninges; namely, the presence of an early acute suppurative leptomeningitis, were not noted in the gross examination, and prob-

ably represent a terminal process similar to that found in conjunction with pneumococcus endocarditis, where a pneumococcus meningitis is an almost invariable terminal finding.

#### PROGNOSIS AND TREATMENT

The usually fatal course of gonococcus endocarditis seems well established. Recovery was reported in several cases noted by Thayer, and in a few recent instances. Perry<sup>3</sup> records the case of a young man with a gonococcus bacteremia proved by blood culture, with the physical signs of a pulmonary valvulitis, from which repeated emboli were discharged to the lungs. The patient experienced a very severe reaction following vaccine therapy, which was consequently discontinued; but after the use of repeated small blood transfusions he recovered, the total course of his disease being three and a half months. Jagié and Schiffner<sup>7</sup> report 3 cases of so-called gonococcus myocarditis, characterized by constitutional signs of septicemia, dilatation of the heart demonstrated orthodiagrammatically, and cardiac irregularities. All recovered, but details as to methods of treatment, aside from that of the primary local condition, are lacking. Gonococcus vaccine has been extensively employed, mostly without any beneficial result. Aubertin and Gambillard<sup>8</sup> treated a case unsuccessfully with antigonococcic serum. Kramer and Smith<sup>9</sup> report 2 cases in which sudden death followed six to ten hours after the intravenous injection of mercurochrome; no autopsy was obtained in these cases, and the diagnosis, although strongly presumptive, was unconfirmed by blood culture. One of McCants<sup>10</sup> patients, treated by intravenous mercurochrome, died suddenly, apparently of a ruptured heart, but autopsy proof was lacking. Electrargol<sup>11</sup> and intravenous metaphen<sup>12</sup> are examples of other therapeutic agents unsuccessfully tried by other authors.

#### NOTES ON CASES FROM RECENT LITERATURE

The 12 cases submitted in the present summary are indicated by asterisks in the list of references. Riecker's<sup>13</sup> case had its onset seven weeks after the urethritis, an unusually long period. The case of Grenet *et al.*<sup>14</sup> was a nine-year-old girl who had been in the habit of sleeping with a sister who had an active gonorrheal vaginitis; in this case meningitis was also present, due to the gonococcus, the differentiation having been conclusively proved by sugar reactions. The case of Lion and Levy-Bruhl was diagnosed in life by a positive agglutination for gonococcus, this being confirmed after death by cultural methods. Lefebure's<sup>15</sup> case was diagnosed by pure culture from an aspirated purulent pericarditis. A positive complement-fixation reaction was reported in Warfield's<sup>16</sup> case, in which no genital gonorrhea was present at the time of examination. Vigot<sup>17</sup> reports a case of a

man of twenty-nine years dying eight weeks after the onset of urethritis, in which gram-negative diplococci were demonstrated on histological examination of an aortic valve vegetation, all cultures having been negative. McCants<sup>10</sup> found gram-negative diplococci in aspirated pericardial fluid, but cultures were sterile and no autopsy was obtained. Another case reported by the same writer showed a vegetative aortic valvulitis with a purulent pericarditis, but cultures of fluid and blood were negative. The cases of Edwards<sup>18</sup> and of Brebner and Buchanan<sup>19</sup> presented no special features, but carried conclusive bacteriological proof of the diagnosis. One of Pratsikas<sup>20</sup> cases had a positive blood culture for gonococcus during life; another showed gram-negative diplococci on post-mortem culture of a mitral vegetation, but their identity as gonococci was never definitely established.

## SUMMARY

A fatal case of gonococcus endocarditis with detailed autopsy findings is reported. Acute endocarditis followed a urethritis and affected an aortic valve which was already damaged by rheumatism.

In addition to acute vegetative endocarditis of the aortic valve, autopsy revealed chronic productive changes in both mitral and aortic valves, subendocardial abscess with extension to the pericardium, diffuse suppurative and hemorrhagic pericarditis, acute intracapillary glomerular nephritis, acute focal interstitial nephritis, parenchymatous degeneration of the kidneys, infarction and suppuration of the spleen, degeneration and congestion of the liver, suppurative gastritis, pulmonary congestion, bilateral hydrothorax, ascites, conjunctival petechiae, suppurative leptomeningitis, gangrene of the legs, and a decubitus ulcer.

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\*Indicates the twelve cases in the recent literature reviewed and summarized in the body of the paper.

## THE DIAGNOSTIC VALUE OF EPINEPHRINE IN ANGINA PECTORIS\*

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LEVINE, Ernstene and Jacobson<sup>1</sup> have recently advocated the use of epinephrine to differentiate between angina pectoris and other conditions attended by precordial distress. They found that 1 c.c. of a 1/1000 dilution injected subcutaneously reproduced the attack in cases of angina pectoris but not in their control groups. The T-wave in the angina group increased in height in Lead II, whereas in their control group the T-wave decreased. This last observation confirmed that of Clough<sup>2</sup> who found that while epinephrine occasionally increased the T-wave, it decreased the T-wave in all leads in the majority of cases of normals and patients with "irritable hearts." However, the electrocardiographic changes during spontaneous angina pectoris are not similar to those reported by Levine, Ernstene and Jacobson. Thus, Feil and Siegel<sup>3</sup> have recently pointed out that the characteristic change in the electrocardiogram during an attack of angina pectoris is a depression of the S-T segment such as is seen in coronary occlusion. They found a variable change in the T-wave in their cases, viz., flattening, inversion and increase in amplitude. Cowan and Ritchie<sup>4</sup> reported a flattening and inversion of T-wave during the angina attack. Furthermore, Cottrell and Wood, recently reported that in a case in which they tried epinephrine they obtained so severe a reaction, that they warn against the indiscriminate use of this test.

For these reasons the subject was reinvestigated, on a group of six cases of known angina pectoris, on a group of six normal internes and on a case of "irritable heart" with precordial distress, and one of luetic aortitis with precordial distress.<sup>†</sup> In every case the patient was put to rest in the decubitus position for one-half hour before starting the observations. Serial electrocardiograms were made; the blood pressure, heart rate and in some cases the respiratory rate were followed and the subjective symptoms of the patient recorded. As a check, in suitable instances, the patient was subjected to a mild exercise to bring on his symptoms.

The results are assembled in tabular form in Tables I, II and III, and characteristic curves are shown in Figs. 1 to 5. In the normal cases, pre-

\*From the Heart Station, Michael Reese Hospital, Chicago. Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

†One case of an elderly patient, seventy-eight years of age, is not included because only 0.5 c.c. of epinephrine was used. This dose produced no changes whatever in this patient.

TABLE I  
NORMAL CASES

| NAME        | AGE | RESTING<br>B.P.<br>MM HG. | MAXIMUM<br>B.P.<br>MM HG. | PULSE<br>PRESSURE<br>INCREASE<br>MM HG. | HEART<br>RATE<br>INCREASE<br>PER MIN. | CONTROL<br>EKG  | CHANGE IN S-T<br>SEGMENT |           |            |               | CHANGE IN T-<br>WAVE |            |   |  | REMARKS |
|-------------|-----|---------------------------|---------------------------|---|---------------------------------------|---|--------------------------|-----------|------------|---------------|----------------------|------------|---|--|---------|
|             |     |                           |                           |   |                                       |   | LI<br>MM                 | LII<br>MM | LIII<br>MM | LI<br>MM      | LII<br>MM            | LIII<br>MM |   |  |         |
| Dr.<br>G.   | 26  | 118/82                    | 122/55                    | 21                                      | 14                                    | QRS slurred all<br>leads, Q <sub>2</sub> and <sub>3</sub> T <sub>1</sub><br>large, T <sub>3</sub> neg., S-T <sub>1</sub><br>and <sub>2</sub> positive | ±0                       | -½        | -½         | +1<br>-1<br>— | -1                   | ±0         | 1 c.c. used, palpitation, max.<br>effect 11 min.  |  |         |
| Dr.<br>Sto. | 31  | 110/62                    | 124/60                    | 16                                      | 4                                     | QRS <sub>2</sub> slurred, T <sub>3</sub><br>small, S-T <sub>1</sub> and <sub>2</sub><br>positive  | ±0                       | ±0        | ±0         | -1            | -1                   | -½         | 1 c.c. used, throbbing in<br>temple, max. effect 12 min.  |  |         |
| Dr.<br>Se.  | 25  | 114/62                    | 128/48                    | 28                                      | 24                                    | QRS slurred all<br>leads, small, Q <sub>2</sub> pre-<br>sented, T <sub>3</sub> small and<br>inverted  | ±0                       | ±0        | ±0         | -1            | -½                   | ±0         | 1 c.c. used, palpitation, dis-<br>comfort and sticking pain<br>over sternum, max. effect<br>20 min. |  |         |
| Dr.<br>W.   | 26  | 110/70                    | 130/70                    | 20                                      | 8                                     | QRS <sub>2</sub> slurred, Q <sub>3</sub> , T <sub>3</sub><br>neg., S-T <sub>2</sub> neg.  | ±0                       | ±0        | ±0         | -1            | -½                   | ±0         | 1 c.c. used, palpitation, max.<br>effect 18 min.  |  |         |
| Dr.<br>Sto. | 28  | 125/85                    | 140/70                    | 30                                      | 32                                    | QRS <sub>2</sub> and <sub>3</sub> slurred,<br>QRS <sub>3</sub> small, S-T <sub>1</sub><br>and <sub>2</sub> positive                                   | -1                       | -1        | -½         | -1½           | -1                   | -½         | 1 c.c. used, palpitation, pre-<br>cordial distress, abdominal<br>distress, max. effect 25 min.      |  |         |
| Dr.<br>E.   | 23  | 110/65                    | 120/60                    | 15                                      | 16                                    | QRS <sub>3</sub> small and<br>slurred, T <sub>3</sub> small,<br>S-T <sub>1</sub> and <sub>2</sub> positive  | -1                       | -½        | ±0         | -1            | -1½                  | -½         | 1 c.c. used, palpitation, max.<br>effect 24 min.  |  |         |

- Indicates a change in a downward direction.

+ Indicates a change in an upward direction.

TABLE II  
ABNORMAL CASES (NOT ANGINAL)

| NAME  | AGE | RESTING<br>B.P.<br>MM HG. | MAXIMUM<br>B.P.<br>MM HG. | PULSE<br>PRESSURE<br>INCREASE<br>MM HG. | HEART<br>RATE<br>INCREASE<br>PER MIN. | CONTROL<br>EKG   | CHANGE IN S-T<br>SEGMENT |           |            |          |           |            | CHANGE IN T-<br>WAVE |           |            |  |  |   | REMARKS |
|-------|-----|---------------------------|---------------------------|---|---------------------------------------|--|--------------------------|-----------|------------|----------|-----------|------------|----------------------|-----------|------------|--|--|---|---------|
|       |     |                           |                           |   |                                       |  | LI<br>MM                 | LII<br>MM | LIII<br>MM | LI<br>MM | LII<br>MM | LIII<br>MM | LI<br>MM             | LII<br>MM | LIII<br>MM |  |  |   |         |
| R.W.* | 67  | 153/90                    | 158/78                    | 17                                      | 12                                    | QRS <sub>2</sub> and <sup>a</sup> inverted, slurred all leads, T small all leads, T <sub>3</sub> neg., S-T <sub>1</sub> and <sup>a</sup> neg., S-T <sub>3</sub> positive | ±0                       | -½        | ±0         |          |           |            | +½                   | ±0        | -½         |  |  | 1 c.c., max. effect 10 min.<br>Pain in middle of sternum and precordium for 15 min.             |         |
| C.T.† | 29  | 138/84                    | 160/80                    | 18                                      | 28                                    | QRS <sub>2</sub> and <sup>a</sup> slurred, small Lead III  | -½                       | -1½       | -1         |          |           |            | -½                   | -1        | -½         |  |  | 1 c.c., max. effect 16 min.<br>Palpitation, ache in thumb, exercise produced more marked effect |         |

\*R. W.—Luetic aortitis.

†C. T.—“Irritable heart.”

- Indicates a change in a downward direction.

+ Indicates a change in an upward direction.

TABLE III  
ANGINA CASES

| NAME | AGE | RESTING<br>B.P.<br>MM HG. | MAXIMUM<br>B.P.<br>MM HG. | PULSE<br>PRESSURE<br>INCREASE<br>MM HG. | HEART<br>RATE<br>INCREASE<br>PER MIN. | CONTROL<br>EKG  | CHANGE IN S-T<br>SEGMENT |           |           |          |           |           | CHANGE IN T-<br>WAVE |           |           | REMARKS   |
|------|-----|---------------------------|---------------------------|---|---------------------------------------|---|--------------------------|-----------|-----------|----------|-----------|-----------|----------------------|-----------|-----------|---|
|      |     |                           |                           |   |                                       |   | LI<br>MM                 | LII<br>MM | LIH<br>MM | LI<br>MM | LII<br>MM | LIH<br>MM | LI<br>MM             | LII<br>MM | LIH<br>MM |   |
| R.P. | 48  | 134/86                    | 138/72                    | 18                                      | 12                                    | QRS <sub>2</sub> small, QRS <sub>3</sub> inverted, QRS slurred all leads, T small all leads           | ±0                       | ±0        | ±0        | -1       | +½        | +½        | -1                   | +½        | +½        | 1 c.c. used, max. effect 30 min. aur. and vent. extrasystoles produced. No complaints.                                    |
| J.G. | 62  | 150/90                    | 195/90                    | 45                                      | 4                                     | QRS slurred all leads, T <sub>1</sub> small, T <sub>2</sub> and <sub>3</sub> neg., S-T neg. all leads | -½                       | ±0        | +½        | +½       | ±0        | +½        | +½                   | ±0        | +½        | 1 c.c. used, max. effect 35 min. Heart conscious.   |
| M.C. | 47  | 130/80                    | 140/80                    | 10                                      | 24                                    | QRS slurred all leads, QRS <sub>2</sub> small, QRS <sub>3</sub> inverted, S-T <sub>1</sub> positive   | -1½                      | -1        | -½        | -2       | -1        | +1        | -2                   | -1        | +1        | 1 c.c. used, max. effect 30 min. pain in abdomen and chest for 2½ hrs., nitrites not used.                                |
| P.J. | 42  | 140/84                    | 146/86                    | 4                                       | 16                                    | QRS slurred all leads, Q <sub>3</sub> , T <sub>3</sub> neg., S-T <sub>2</sub> and <sub>3</sub> neg.   | -1                       | -1        | ±0        | -1       | -½        | +½        | -1                   | -½        | +½        | 1 c.c. used, max. effect 16 min. No pain, yet a preliminary exercise brought on pain and more marked similar EKG changes. |
| H.W. | 47  | 155/95                    | 175/105                   | 10                                      | 20                                    | QRS slurred and small all leads   | -1                       | -1        | -½        | -1       | -1½       | -1        | -1                   | -1½       | -1        | 1 c.c. used. max. effect 29 min. Precordial pain, relieved by nitrites.   |

- Indicates a change in a downward direction.

+ Indicates a change in an upward direction.

TABLE III (CONTINUED)  
ANGINA CASES

| NAME                | AGE | RESTING<br>B.P.<br>MM HG. | MAXIMUM<br>B.P.<br>MM HG. | PULSE<br>PRESSURE<br>INCREASE<br>MM HG. | HEART<br>RATE<br>INCREASE<br>PER MIN. | CONTROL<br>EKG   | CHANGE IN S-T<br>SEGMENT |           |            |          | CHANGE IN T-<br>WAVE |            |                                 | REMARKS   |
|---------------------|-----|---------------------------|---------------------------|---|---------------------------------------|--|--------------------------|-----------|------------|----------|----------------------|------------|---------------------------------|---|
|                     |     |                           |                           |   |                                       |  | LI<br>MM                 | LII<br>MM | LIII<br>MM | LI<br>MM | LII<br>MM            | LIII<br>MM |                                 |   |
| W.P.<br>1st<br>test | 34  | 135/90                    | 155/90                    | 20                                      | 34                                    | QRS slurred all<br>leads, Q <sub>3</sub> , T <sub>1</sub> large,<br>T <sub>3</sub> neg., S-T <sub>3</sub> neg. | -½                       | -1½       | -1         | -1½      | -1                   | -½         | T <sub>3</sub> more<br>inverted | ½ c.c. used, max. effect 15<br>min. Extrasystole felt at<br>wrist after epinephrine, but<br>not recorded. Tightening<br>of chest and pain lasted 41<br>min. Unrelieved by nitrites. |
| 2nd<br>test         |     | 124/78                    | 140/78                    | 16                                      | 28                                    | QRS slurred all<br>leads, Q <sub>3</sub> , T <sub>2</sub> tiny,<br>T <sub>3</sub> neg., S-T <sub>2</sub> neg.  | -½                       | -½        | -½         | -½       | -½                   | -½         | ±0                              | 1 c.c. used, max. effect 15<br>min. Aur. extrasystole in-<br>duced pain and tightening<br>in chest radiating to rt.<br>side—lasted 30 min.  |
| 3rd<br>test         |     | 118/86                    | 174/100                   | 42                                      | 32                                    | QRS slurred all<br>leads, Q <sub>3</sub> , T <sub>3</sub> neg.,<br>S-T <sub>2</sub> and <sub>3</sub> neg.      | -1                       | -1½       | -½         | -1½      | -1                   | +1½        | T <sub>3</sub> iso-<br>electric | 1 c.c. used, max. effect 15<br>min. T <sub>3</sub> became isoelectric.<br>Pain in abdomen and slight<br>in chest. Exercise caused<br>similar but more marked<br>changes.            |

- Indicates a change in a downward direction.

+ Indicates a change in an upward direction.

cordial distress was noted in two of the six subjects following adrenalin. In the angina cases three of the six patients had no pain, although in one of them a typical pain attack was produced by exercise. Of the two abnormal cases (not anginal), one had an attack of pain over the precordium while the other did not. It would seem from these results that the production of pain by epinephrine is not a reliable sign of angina pectoris. Furthermore, the pain when produced in two of three angina cases was long lasting and upset the patients greatly, and in one was not checked by nitroglycerine. Even in the normal cases, one of the subjects had a severe symptomatic reaction presumably because of a susceptibility to epinephrine.

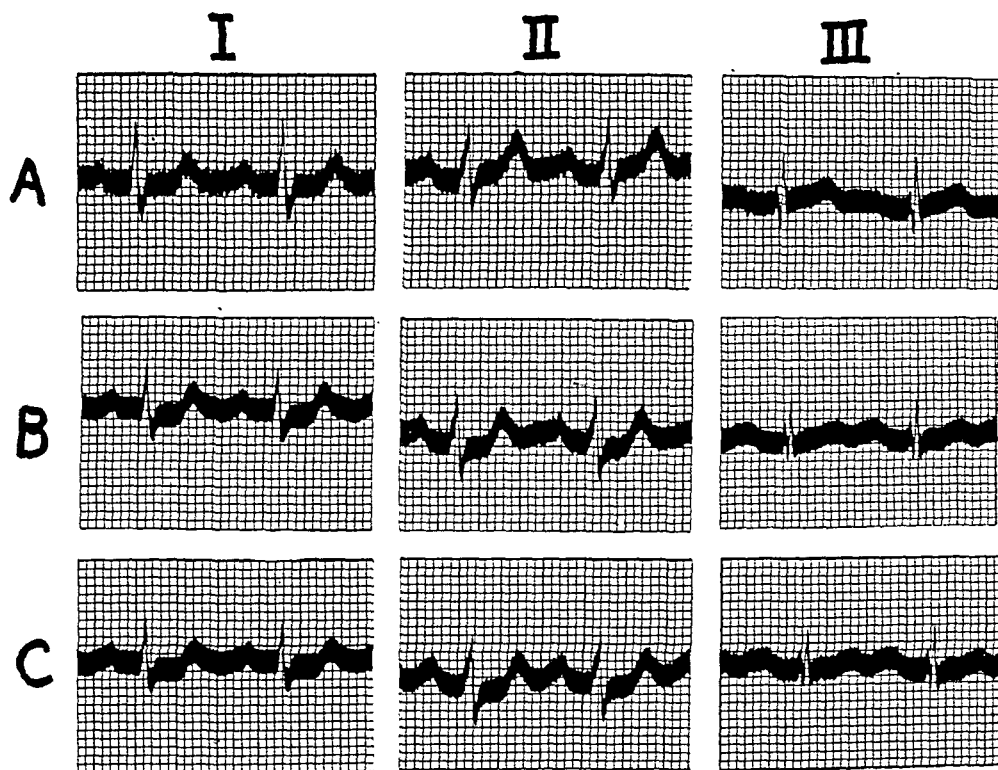


Fig. 1.—Effect of epinephrine on the electrocardiogram of a patient (M.W.) with angina pectoris. *A*, control; *B*, eleven minutes; *C*, nineteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

The most characteristic electrocardiographic change produced by epinephrine in the angina cases was a deviation downward of the S-T interval which gave the electrocardiogram an appearance similar to that seen during spontaneous attacks of angina (Figs. 1 and 2). In one case, however, even this change was absent. However, a similar change was seen in the patient with the "irritable heart" (Fig. 4). In several of the normal subjects, the S-T interval was found to be slightly positive normally and the epinephrine tended to depress it to the isoelectric level or beyond (Fig. 5). It would seem, therefore, that qualitatively there is little difference in the effect on angina patients and others, although

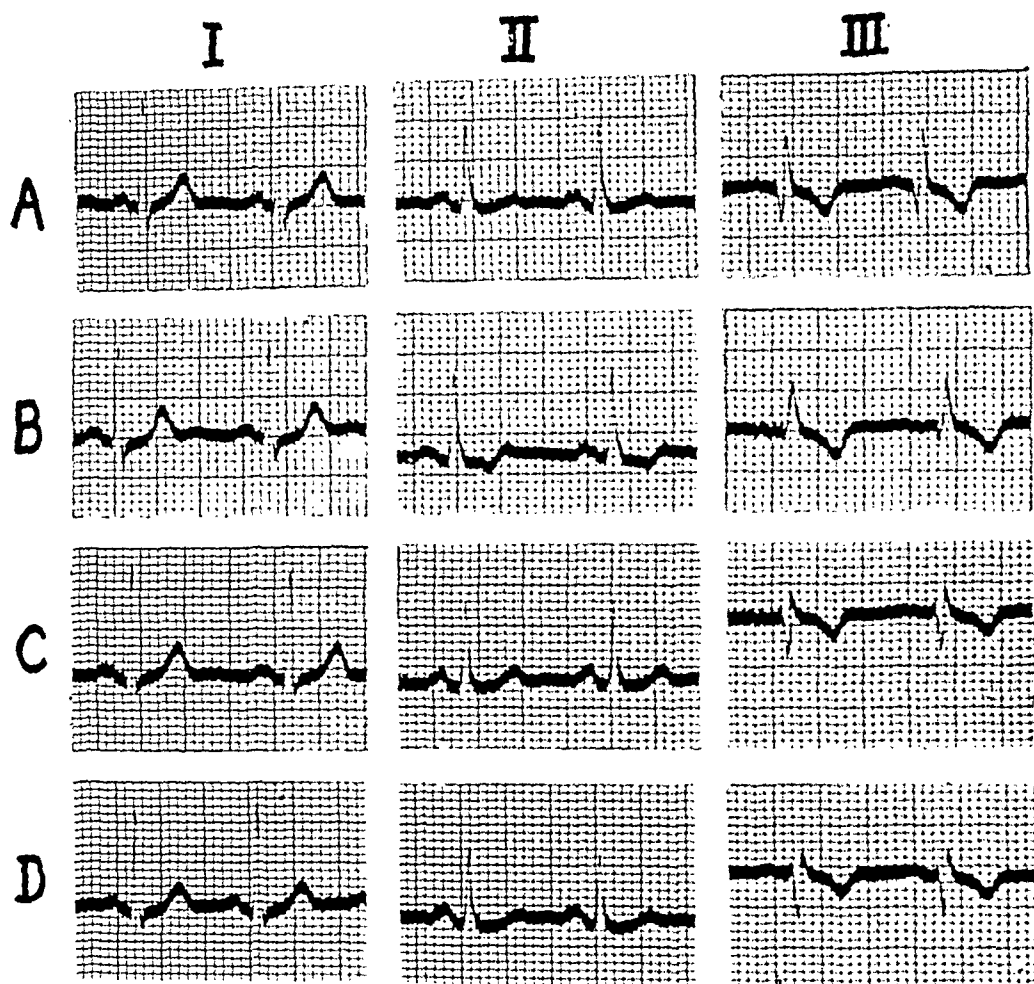


Fig. 2.—Effect of exercise and epinephrine on the electrocardiogram of a patient (P.J.) with angina pectoris. *A*, control; *B*, after standing run which brought on an attack of angina pectoris; *C*, forty minutes later after rest in bed; *D*, sixteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

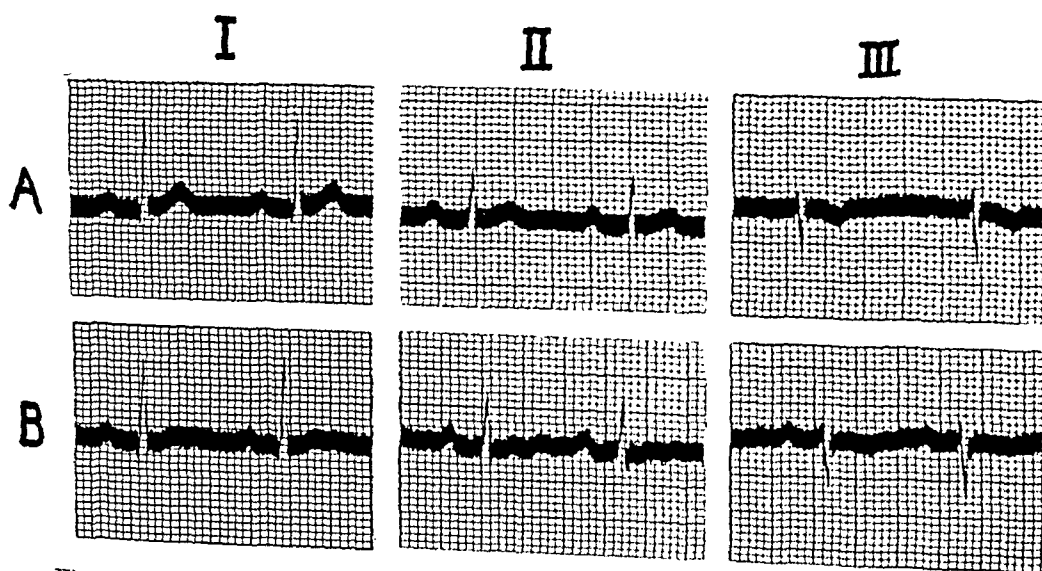


Fig. 3.—Effect of epinephrine on the electrocardiogram of a patient (M.C.) with angina pectoris. *A*, control; *B*, twenty-one minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.



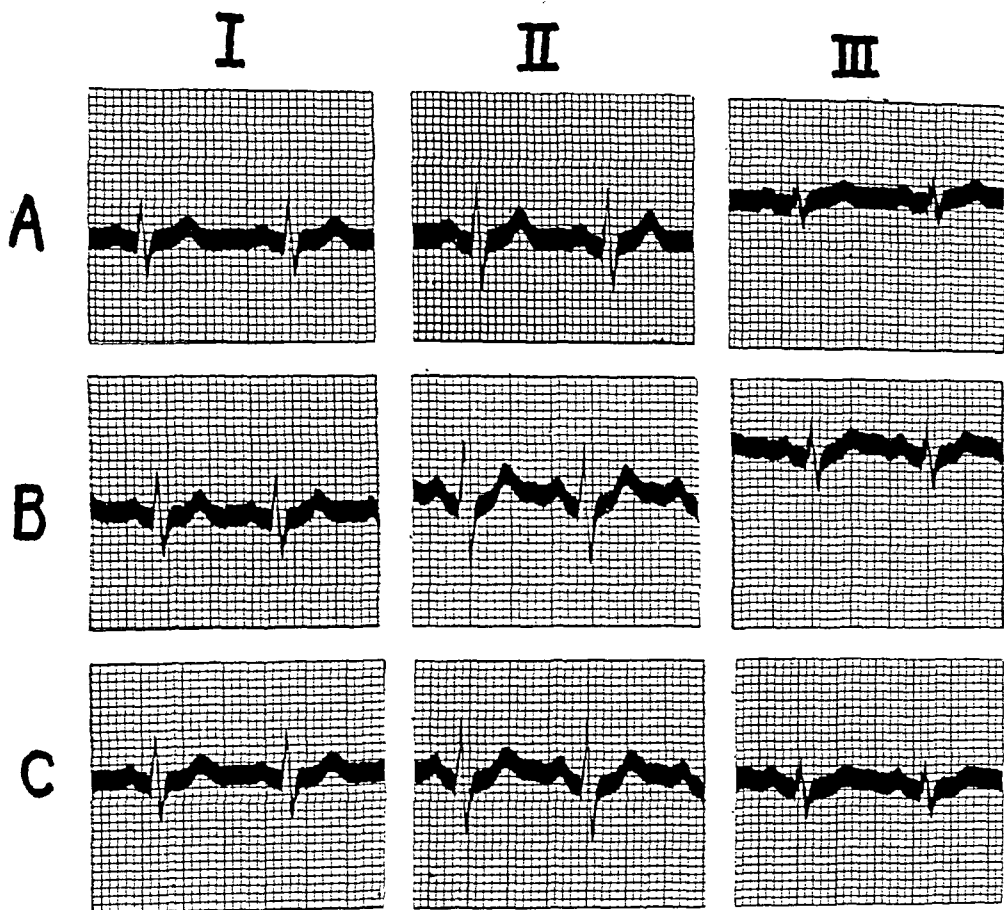


Fig. 4.—Effect of epinephrine on the electrocardiogram of patient (C.T.) with an "irritable heart." A, control; B, seven minutes, and C, fourteen minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

quantitatively the effect was more marked in the angina patients. The effect of epinephrine on the T-wave was to decrease the amplitude of the wave in practically all the cases, normals as well as angina cases (Figs. 1, 2, 3, 4 and 5) even when the T-wave was inverted to start with (Fig. 3, Lead III). However, in two cases of angina when there was a noticeable left axis shift to start with, the T-wave in Lead III became more upright. In the majority of cases the duration of T decreased.

From these results it seems that the change in the electrocardiogram produced by epinephrine also is unreliable as a test of angina pectoris, although in many cases of angina the change in the S-T segment during epinephrine administration was similar to that occurring during spontaneous attacks of angina pectoris and during those induced by exercise.

The reaction of the blood pressure and heart rate was the same in angina cases and in others except that a drop in diastolic pressure was seen less often in the angina cases (Tables I, II and III).

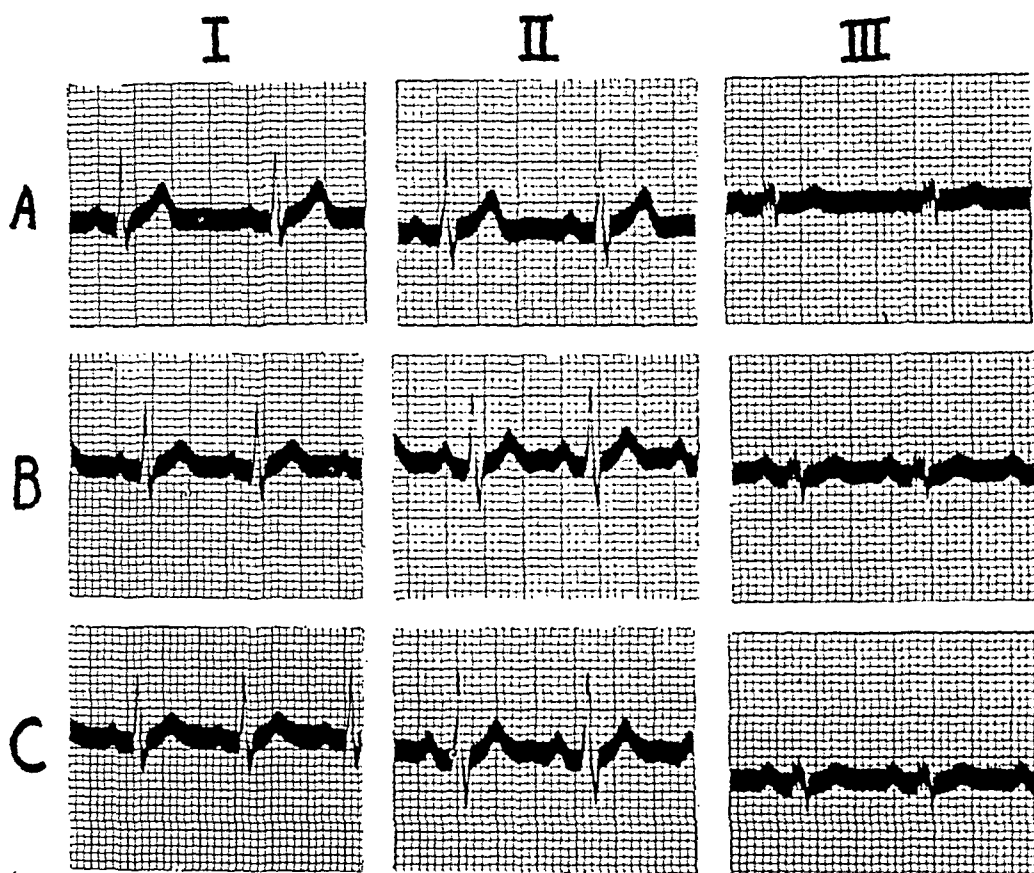


Fig. 5.—Effect of epinephrine on the electrocardiogram of a normal individual (Dr. Ste.) A, control; B, eight minutes, and C, twenty-five minutes after subcutaneous injection of 1 c.c. of 1/1000 epinephrine.

#### SUMMARY

Epinephrine as a test for angina pectoris was found to be unreliable in regard to both the symptoms produced and the electrocardiographic changes. This unreliability makes the test of little value, particularly in view of the severe reactions sometimes encountered.

We are indebted to Dr. S. H. Rubinfeld for assistance and to the six internes who subjected themselves to the test as controls.

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# A CHART FOR THE DIFFERENTIAL DIAGNOSIS OF CARDIAC ENLARGEMENT BY MEANS OF THE ROENTGEN RAY\*

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IN THE roentgen study of heart disease it is found that distinctive lesions are frequently associated with characteristic changes which can be seen on the film. Tabulation of these changes enhances their

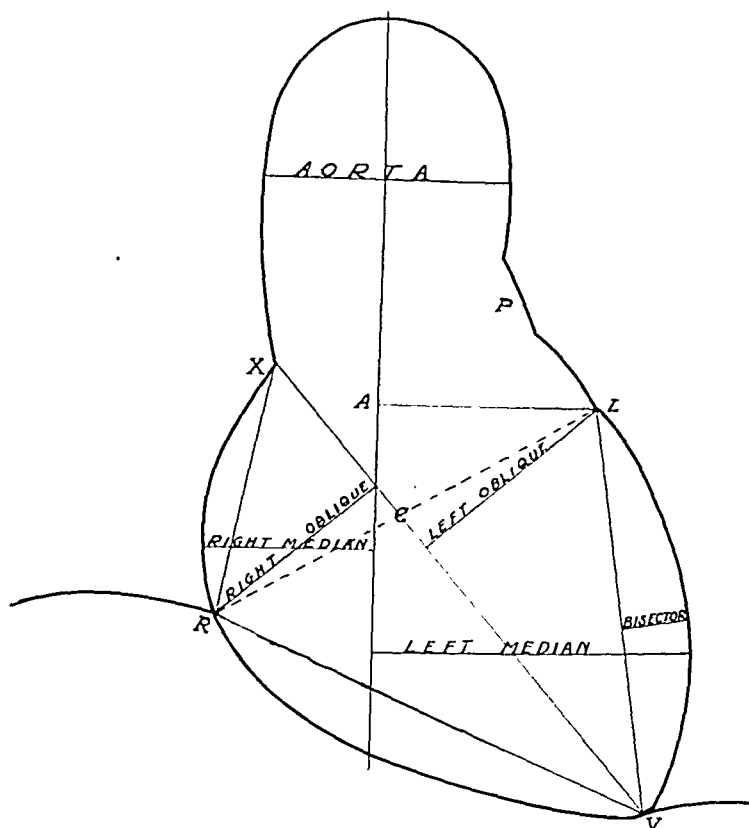


Fig. 1.—LA, left auricle; LV, left ventricle; RV, right ventricle; RX, right auricle;  $CX \div CV$  = index of auricular ventricular ratio; right median + left median = transverse; VX, length; P, pulmonary artery.

identification with clinical cardiopathies. The chart is presented to facilitate this tabulation and to indicate a presumptive roentgen diagnosis.

Observations are based both on fluoroscopic studies and on measurements of the teleroentgenogram. The measurements, many of which were derived by Vaquez and Bordet<sup>1</sup> from anatomic landmarks are illustrated in Fig. 1. A line running through the center of the spinous processes serves as a base line. Perpendiculars to this line from the point of greatest distance on the right and on the left, establish the right and left median diameters (or transverse diameter) of the heart.

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TABLE I  
DIFFERENTIAL ROENTGEN DIAGNOSIS OF CARDIAC ENLARGEMENT

|                         | PULMONARY ARTERY | RIGHT VENTRICLE | TRANSVERSE DIAMETER | LEFT VENTRICLE | BISECTOR    | LENGTH        | AORTIC PULSATIOMS | AORTIC WIDTH | INDEX OF AURICULO-VENTRICULAR RATIO | LEFT AURICLE | RIGHT AURICLE | REMARKS   |
|-------------------------|------------------|-----------------|---------------------|----------------|-------------|---------------|-------------------|--------------|-------------------------------------|--------------|---------------|---|
| Normal values           |                  | 8.5-<br>14.7    | 9.5-<br>14.5        | 6.7-<br>8.5    | 0.6-<br>1.0 | 11.5-<br>15.0 |                   | 4.0-<br>6.5  | 0.534-<br>0.704                     | 4.2-<br>5.0  | 5.0-<br>6.5   |   |
| Pulmonary stenosis      | X                | X               | X                   | X              |             | X             |                   |              |                                     |              |               | Anatomically shadow may be pulmonary artery or infundibulum. Neither should exceed that of left auricle. Left ventricle not enlarged. |
| Mitral insufficiency    |                  | X               | X                   | X              | X           |               |                   |              |                                     | X            |               | Enlargement of heart is transverse.   |
| Tricuspid insufficiency |                  | X               |                     |                |             |               |                   |              |                                     |              |               | Secondary evidence: hepatic and pulmonary congestion.   |
| Aortitis                |                  |                 |                     |                |             |               | X                 | X            |                                     |              |               | Knob flattened and broadened. Curve of ascending aorta diminished.  |
| Aortic stenosis         |                  |                 |                     |                | X           | X             |                   |              |                                     |              |               | Pulsations of aorta are diminished. Con-  |
| Hypertension            |                  |                 |                     | X              | X           | X             | X                 |              |                                     |              |               | tractions of left ventricle increased.  |
| Aortic insufficiency    |                  |                 |                     | X              | X           | X             | X                 | X            |                                     |              |               | Accentuated curve of ascending aorta.   |
|                         |                  |                 |                     |                |             |               |                   |              |                                     |              |               | Coeur bovinum. Heart shadow centrally placed.   |
| Mitral stenosis         |                  | X               | X                   | X              | X           | X             |                   |              | X                                   | X            | X             | Ventricles not enlarged. Apex pointed.  |
| Myxedema heart          |                  |                 |                     |                |             |               |                   |              |                                     | X            |               | Symmetrical enlargement, looks like effu-   |
|                         |                  |                 |                     |                |             |               |                   |              |                                     |              |               | sion. Pulsations are of approximately   |
|                         |                  |                 |                     |                |             |               |                   |              |                                     |              |               | normal amplitude.   |
| Pericardial effusion    |                  | X               | X                   | X              | X           | X             |                   |              |                                     | X            | X             | Symmetrical enlargement, water bottle shape.  |
|                         |                  |                 |                     |                |             |               |                   |              |                                     |              |               | Pulsations are very faint or absent.  |

X = Increased.

A line ( $VX$ ) joining the beginning of the right auricular shadow and the apex measures the length of the heart. Perpendiculars to this line from the cardiophrenic angle ( $R$ ) and the auriculo-ventricular junction ( $L$ ) establish the right and left oblique diameters which show the development of the base of the heart.

If  $VX$  is intersected (at  $C$ ) by a line joining the cardiophrenic angle on the right ( $R$ ) with the auriculo-ventricular junction on the left ( $L$ ), the heart shadow is divided into two areas; auricular area above the line  $RL$  and ventricular area below it. The length of the segment  $CX$  divided by the length of the segment  $CV$  establishes an index of auriculo-ventricular ratio.<sup>2</sup> In normal hearts this varies between 0.534 and 0.704. In the presence of auricular enlargement the index rises to 0.800 or more. When there is preponderant enlargement of the ventricles, the index falls to 0.500 or less.

The lines  $RX$ ,  $RV$ ,  $LV$ ,  $LA$  show respectively the development of the several chambers, viz., right auricle, right ventricle, left ventricle and left auricle.

The bisector, a perpendicular from the point of greatest bulge of the border of the left ventricle to the line measuring its chamber ( $LV$ ), shows the degree of development of the left ventricular myocardium.

In the application of these measurements to the roentgen diagnosis of heart disease (Table I) it will occasionally be found that not all the positive observations which indicate the lesion in question are present. This does not appear to detract materially from the method of analysis and correlation of roentgen findings herein described. If the salient features of a distinctive cardiopathy are found, and particularly if the clinical evidence agrees, a roentgen diagnosis in terms of the valve or chamber involved may be made with confidence.

If the evidence does not establish a definite diagnosis, it may suggest an error in the roentgen measurements, or the chart may not have been correctly used, or the case is too obscure to warrant a positive diagnosis at the present state of our roentgen knowledge.

The chart may suggest that two or more lesions exist. This may well be, since various combinations are often found in the same patient.

The space limitations of a chart preclude extensive and detailed descriptions. An attempt is made to indicate only the distinguishing characteristics of the various heart lesions. A more detailed account has been presented elsewhere.<sup>3, 4</sup>

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# AN INSTRUMENT TO DETERMINE THE DIRECTION OF THE ELECTRICAL AXIS OF THE HUMAN ELECTROCARDIOGRAM\*

BASED ON THE GRAPHIC METHOD OF CARTER, RICHTER, AND GREEN

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IN 1919, Carter, Richter, and Green<sup>1</sup> described a graphic method for determining the direction and "manifest value" of the electrical axis of the human electrocardiogram. The method makes use of the principle of the equilateral triangle described by Einthoven.<sup>2, 3</sup>

By a slight modification, and its application in the form of a handy instrument (Fig. 1), the method has found considerable usefulness in our hands. The angle and manifest potential of an electrical axis can be estimated in a few seconds. The instrument is particularly valuable for teaching purposes, because it makes possible a ready understanding of the principles of the equilateral triangle and also the visualization of the changes of the electrical axis in a cardiac cycle.

The method makes use of a graphic figure in which an equilateral triangle with the base directed upward is enclosed in a circle, the center of which is also the center of the triangle. Beginning at the midpoint of each side, perpendiculars directed to the three sides of the triangle are drawn through its interior at units representing millimeter intervals. The three sides of the triangle represent the three leads. Lead I, which is the base, is divided into right (positive) and left (negative) sides, corresponding to upward and downward deflections of the electrocardiogram. Lead II, the left side, is similarly divided into halves, an upper (positive) and lower (negative), as is also Lead III. In such a geometric system a line extending from the center when projected on the three sides will give a value on the left side (Lead II) which will equal the algebraic sum of the projections on the other two sides. Since Einthoven<sup>3</sup> has shown that this relationship holds for the human electrocardiogram, that is the values of simultaneous points on the three leads are such that  $\text{Lead II} = \text{Lead I} + \text{Lead III}$ ; and since the three leads of the electrocardiogram represent the projections of the electrical axes, by substituting simultaneous values on the three sides of the triangle and reversing or projecting toward the interior, the electrical axis is delineated.

The instrument is made of aluminum. Perpendiculars are drawn only to Leads I and III. It is obviously not necessary to draw them to all three leads. The perpendiculars are extended outside the tri-

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angle to include values exceeding two millivolts. Attached to the center of the triangle is a revolving arm which is divided into units similar to those which divide the sides of the triangle. This arm extends beyond the surrounding circle. The circle is divided into degrees beginning from a point on the right which forms a horizontal with the center. The values below that zero point are arbitrarily called positive, those above, negative.

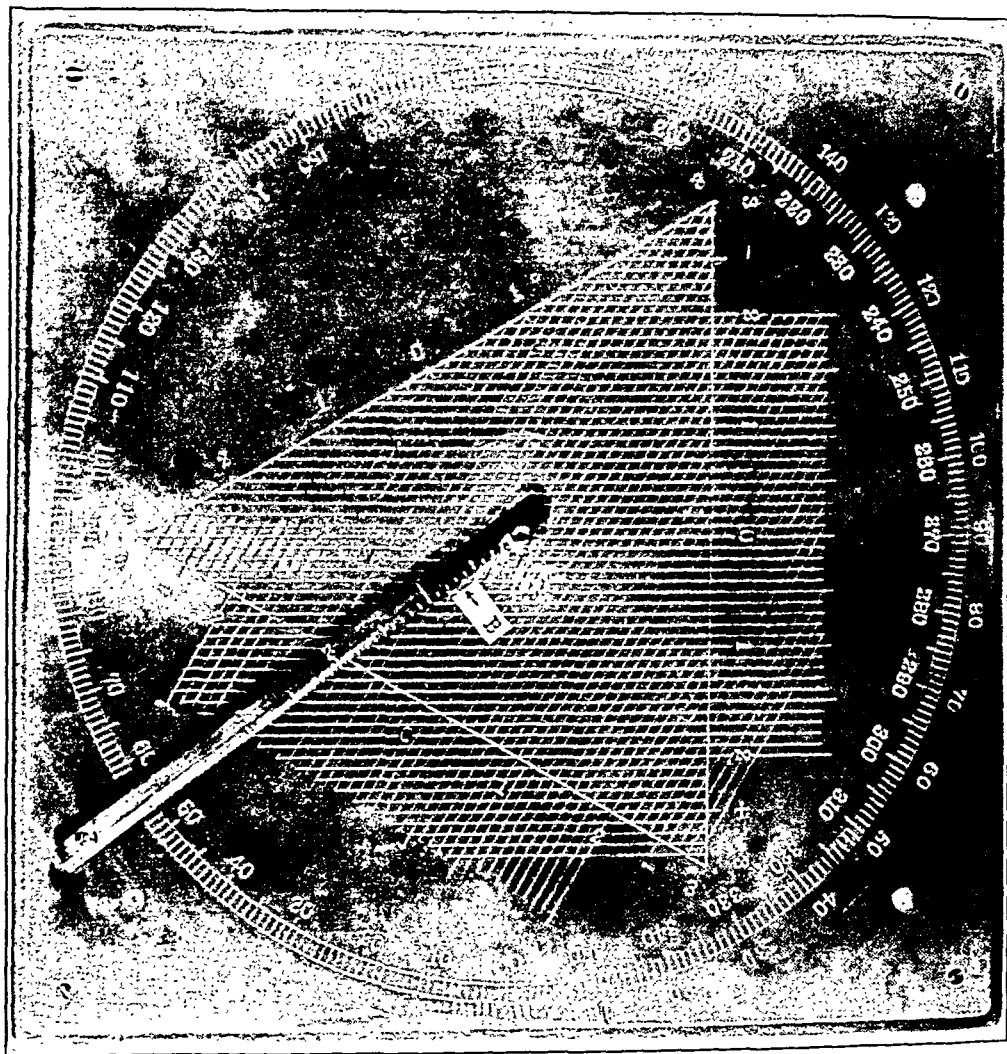


Fig. 1.

Simultaneous values are marked off on Leads I and III. The limits of these values are followed along the perpendiculars. The zero limits will of course intersect at the center, the outer limits will intersect at the outer limit of the electrical axis. By bringing the revolving arm to the point of intersection, the arm will represent the direction of the electrical axis, and on it the value of the manifest potential can be read. The arm will also read off on the circle the degrees the electrical axis makes with the horizontal. Thus, at once both the manifest value and the angle of the electrical axis can be determined.

Example: Points *A* represent simultaneous values on the two leads. Fig. 2.—The electrocardiograms have been standardized so that every centimeter of deflection represents a millivolt. The value of point *A* in Lead I = 4 millimeters (0.4 millivolts) directed upward;

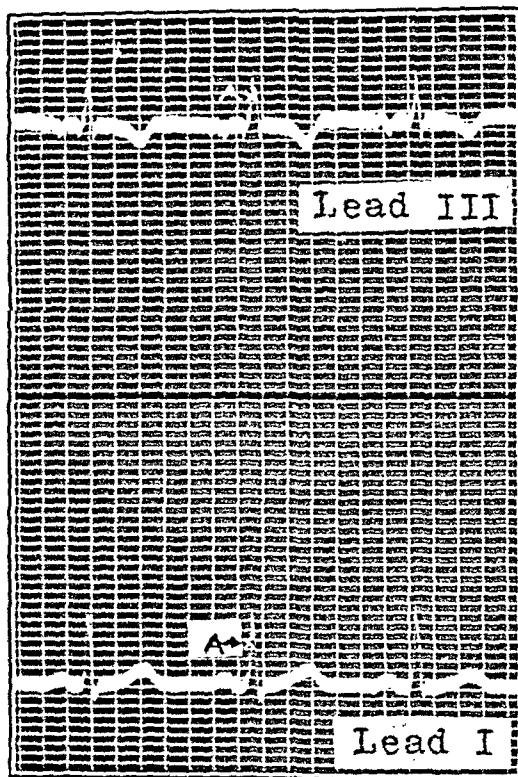


Fig. 2.—Leads I and III taken simultaneously with a Hindle Two Galvanometer Research Model Electrocardiograph. (1/10 second time lines) Lead III top tracing.

therefore measured to the right on the instrument. *A* on Lead III = 3 millimeters (0.3 millivolts) and is also directed upward; therefore measured on the positive side of Lead III. The perpendiculars of these points meet at *B*.

Fig. 1.—By bringing the arm around to the intersection, the manifest value can be read and is equal to 0.7 millivolts. The circle is intersected at  $+53^\circ$ ; i.e. electrical axis directed downward  $53^\circ$  from the horizontal.

The author wishes to express his appreciation to Dr. A. C. De Graff for his aid in this work.

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## Department of Clinical Reports

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### A CASE OF CORONARY THROMBOSIS WITH TEMPORARY COMPLETE HEART BLOCK\*

OLGA S. HANSEN, M.D.

MINNEAPOLIS, MINN.

IN ORDER to add to the records of disturbances of rhythm in coronary thrombosis the following case is reported.

A male laborer, aged seventy-seven years, with a history of anginal attacks for at least nine years, developed an attack of severe substernal pain after lifting a heavy weight. Pallor, fever, leucocytosis and fall in blood pressure led to a diagnosis of coronary thrombosis. A systolic murmur, not present on examinations prior to this illness, appeared and increased in loudness and roughness over the lower precordium and was associated with a prolonged systolic thrill just within the apex. These findings developed to a maximum by the fifth day and persisted until death which occurred suddenly on the twelfth day. Post-mortem examination was not permitted.

The electrocardiograms are of interest in that they show a complete dissociation between auricle and ventricle on the fifth and the eighth day after the onset of the illness, but a normal auriculo-ventricular conduction time (.20 sec.) on the twelfth day shortly before his death. One can surmise the presence of a thrombus extending into the ventricular cavity in such a way as to cause a systolic murmur and thrill, and an involvement of the auriculo-ventricular bundle by an area of transient tissue pathology which developed on the fifth day to a point of blocking impulses, and had again returned to approximately normal function by the ninth day (clinical return to normal pulse rate), proved by electrocardiograms on the twelfth day.

The case is presented because of two points of interest:

1. A rough murmur and thrill developed over the precordium in the early days following a case of coronary thrombosis.
2. Complete heart block developed on the fifth day and disappeared on the ninth, although the patient died suddenly on the twelfth day.

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\*From the Department of Medicine, The Nicollet Clinic.

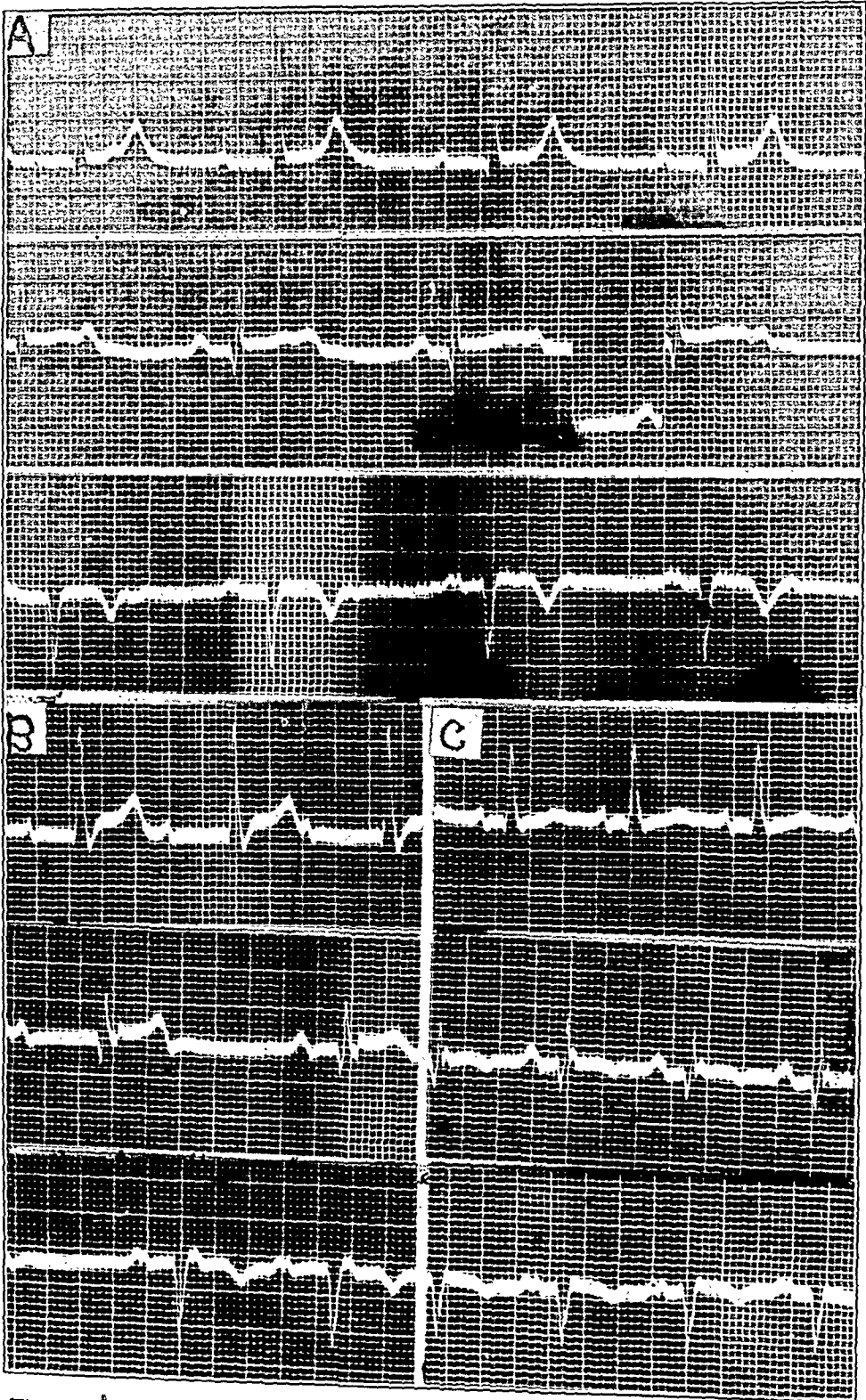


Fig. 1.—A. Nov. 19, 1930 (fifth day of illness). Auricular rate 100, ventricular 56, complete dissociation. B. Nov. 22, 1930 (eighth day). Partial auriculo-ventricular block with missed beats. C. Nov. 26, 1930 (twelfth day). Normal auriculo-ventricular conduction P. R. = .20 sec.

## AN UNUSUAL CASE OF LEFT-SIDED DISPLACEMENT OF THE HEART\*

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BROOKLYN, N. Y.

**D**ISPLACEMENT of the heart from its normal position may be congenital or acquired. Of the congenital displacements, the usual form is dextrocardia, which may be due to simple rotation on a vertical axis, or to complete reversion. Rarer forms are incomplete heterotaxy and ectopia cordis. Of the latter there are three forms, according to Ellis<sup>1</sup>—Cervical, with displacement of the heart to the neck; pectoral, with displacement to the anterior chest wall through a vertical slit in the sternum; and abdominal, with displacement into the abdomen through a congenitally maldeveloped diaphragm.

Of the acquired forms, the displacement may be to the right or left and upward. Because the heart is relatively fixed at the base by the great vessels and relatively free at the apex, displacement, to whatever side it may take place, is more or less rotatory and transverse. The greatest movement is at the lower portion, while the basal area may remain in an approximately normal position but rotated.

The extent and nature of acquired displacement will depend, however, more on the causative factor or factors than on the natural resistance offered by the heart attachments. The causative factors in the main are two: pressure and traction. The first includes certain bony deformities of the chest, and some forms of mediastinal and pleuropulmonary disease, such as hydrothorax, pneumothorax, tumors, aneurysms, emphysema, and others. The second includes pleuropericardial adhesions reaching the bony part of the thoracic cavity and extensive enough to overcome the natural resistance to displacement.

The differentiation between congenital and acquired displacement is based upon the character of displacement, associated pathological states, and duration. Acute displacements are easily recognized as acquired. Chronic displacements attributable to adhesions or bony protuberances are likewise easily recognized as acquired by associated chest deformity. When no such pathological conditions are found, the condition may be considered congenital, although in rare cases with a history of thoracic injury in early life, the question of etiology may remain unanswered.

The following case is presented because of its extreme rarity, and of some doubt as to its etiology.

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\*From the Department of Medicine, New York Post Graduate Medical School of Columbia University.

## CASE REPORT

D. E., male, fifty years old, came to the cardiac clinic of the Harbor Hospital with complaints of occasional pain in the left side of the chest radiating to the left lower scapular region, for the past eight months. The pain had no relation to exertion, was of short duration and mild character. His family history was irrelevant. His personal habits were always regular. He married twenty years ago, had had four children, one of whom died at eight months from some acute disease; the others are well.

A point of interest in his history is that at seven years of age he fell from a third story window and was laid up for several months, the outstanding symptom which he can remember being severe cough. He did not know the real nature of his injuries. Since then, however, he enjoyed perfect health, always working hard, and but once had the "grip" for several days. He was told about thirty years ago that there was something wrong with his heart.



Fig. 1.—Antero-posterior view of the chest. Arrows 1 show the trachea and primary bronchi. Arrow 2 shows the esophagus. Arrow 3 shows the spine. Arrows 4 show the heart and great vessels. The heart, great vessels, trachea, primary bronchi, and esophagus are displaced to the left of the spinal column. The esophagus is seen to approach the center of the spine in its descent. The spine is seen to run somewhat obliquely from above downward and to the left.

The physical examination revealed a well-developed, robust male, of good nutrition and normal color. His pupils reacted normally, and his nose, mouth, throat, and neck were negative. His chest was of normal shape and size, with no bulgings, retractions, deformities, or abnormal pulsations. The lungs were negative, and normal vesicular resonance was heard even over the area which in normal persons is occupied by superficial cardiac dullness. No cardiac dullness was elicited over the normal precordial area, and no visible or palpable apex impulse was present anywhere over the anterior chest. Examination of the left axilla revealed an area of visible and palpable pulsation, about two inches wide in the midaxillary line between the sixth and eighth ribs, and extending from four centimeters from the spine posteriorly to the anterior axillary line. No systolic retraction of the chest wall in this region was visible. The first heart sound was heard best at the area of maximum pulsation, while the second sound was heard best two inches higher. The sounds were of normal intensity and character, and could be heard well throughout the area of dullness. No sounds were heard over the area of the

posture of the patient changed the heights of the complexes and to some extent also their direction. The greatest change in direction occurred when the patient was placed in the right lateral position.

#### COMMENT

A perusal of the literature failed to show a similar case of sinistocardia, although numerous cases of dextrocardia are on record. Acquired sinistocardia, due to well-recognized pathological processes does occur, and has been recently described by D'Hour.<sup>2</sup> The underlying cause or causes can, however, be demonstrated in such cases. Besides, in acquired sinistocardia the heart is placed more transversely, the basal vessels remaining in a more or less normal position, unless they are pushed aside by a big tumor mass in the mediastinum, a condition easily recognizable clinically and on roentgenologic study.

In our case there were absolutely no signs of circulatory impediment or gross pathology of sufficient extent to produce such displacement. Although there is a history of injury in early life with resulting illness for several months, there were no signs of pleuropericardial adhesions to be found on physical, fluoroscopic, and electrocardiographic study, which might be taken as an indication that injury was the cause of this unusual displacement. Although the spine is somewhat obliquely placed, it likewise cannot be considered to be the cause of the displacement, the obliquity being rather opposite in direction to that of the displacement.

From the nature of displacement, involving other mediastinal structures; from its long duration, the patient having been told thirty years ago that "there was something wrong with his heart"; and, from the fact that there was no circulatory or respiratory embarrassment that might be caused by an acquired lesion; also, from the absence of any signs of adhesions, we may conclude that the condition is congenital. As such, there is to my knowledge no other similar case reported. There is one case reported of a congenital defect of the left wall of the pericardial sac<sup>3</sup> with sudden death caused by sudden displacement of the heart through that opening, into the left pleural cavity, during labor. Until this accident the patient was apparently perfectly normal all her life.

The peculiar behavior of the electrocardiogram in the various leads may be accounted for by the fact that the electrical axis does not bear the normal relationship to the standard leads in this case, due to rotation and displacement.

#### SUMMARY

A case of sinistocardia, most likely congenital, is reported, which from perusal of the literature appears to be the only one of its kind on record. The outstanding features in the case are: (a) Healthy male,

fifty years old, who had gone through life without any circulatory or respiratory embarrassment; (b) the heart with its basal vessels was entirely displaced to the left of the spinal column; (c) other mediastinal contents, such as the esophagus, trachea, and bronchi were likewise displaced. Although a history of injury is given, it seems to be a mere coincidence, as there is no definite evidence of a pathologic condition present, the nature of which might be considered to be the cause of the displacement.

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## SAMOILOFF AND HEITZ

### EMINENT CONTRIBUTORS TO CARDIOVASCULAR LITERATURE

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#### ALEXANDER PHILIP SAMOILLOFF. 1867-1930.

A distinguished worker in the physiology of muscle and nerve and a pioneer in electrocardiography was Professor Alexander Philip Samoiloff of Kasan, U.S.S.R. (Russia), whose death was an unhappy surprise to his many friends the world over. Not only because of his eminence in cardiology but also because of his wide acquaintanceship it is a pleasant duty to publish for his English-speaking friends, and for others too, who may read this JOURNAL, a brief account of his life and accomplishments. Last year in Russia a memorial number of the *Kasan Medical Journal* was published in honor of Professor Samoiloff (April-May, 1931, No. 4-5); the first article was an appreciation by Professor Pavlov of Moscow with whom Samoiloff had at one time worked. This brings to mind a somewhat similar reminiscence in the AMERICAN HEART JOURNAL in June, 1930, by Professor Samoiloff himself of Einthoven, the inventor of the string galvanometer, whose death occurred in 1927.

Alexander Philip Samoiloff was born in Odessa in 1867. He attended a government high school and then the University of Odessa, from which he was graduated in 1888 as a Bachelor of Natural Science. He entered the Medical School of the University of Derpt the same year, was graduated in 1891, submitted his thesis in 1892, and was thereupon awarded the degree of Doctor of Medicine. For a few months he practiced medicine in Odessa and then spent another few months working in a severe epidemic of cholera in Siberia. From 1893 to 1894 he was assistant to Professor Pavlov at the Institute of Experimental Medicine in Petrograd where he devised some improvements in technic in the operations on animals whose digestive functions were being studied by means of fistulas, and where he made a thorough investigation of Mett's method for the determination of certain ferments. In 1894 to broaden his experience and training Samoiloff transferred to the University of Moscow where he became assistant to Professor Schechinoff who was particularly interested in physical and chemical methods of physiological study. It was here that Samoiloff became interested in physiological physics which led him to spend the rest of his life studying the manifestations, and in particular the electrical manifestations, of the action of muscle and nerve. When Professor Samoiloff was in Boston a few years ago, he gave an address at the Massachusetts General Hospital in the course of which he referred to the importance of physiological studies on heart

muscle, not only for their own value but also because they had proved so often to be pioneer steps in similar studies on other muscle and on nerve tissue.

In 1896 Samoiloff was appointed Associate Professor of Physiology at the University of Moscow and for the next seven years he conducted a part of the course in physiology for the students of the school of medicine and of the school of natural science. In 1903 he was appointed full Professor of Physiology at the University of Kasan in eastern Russia and continued in that position until his death in 1930, although during the last few years he travelled to Moscow frequently to give lectures at the University there to supplement the course in physiology. He always responded to such calls of duty and made especial efforts to keep in touch with his colleagues in physiology in other parts of the world in spite of the great difficulties that surrounded him during and after the Russian revolution. This is attested by his attendance in late years at the International Physiological Congresses in Stockholm in 1926 and in Boston in 1929. It was during his two visits to America in 1926 and 1929 that I derived much pleasure and stimulation from contact with Professor Samoiloff and from acquaintance with his family. Two sons, twin youths, have settled down in America as engineers to carry on the professional activities of the family, while Madame Samoiloff and an older daughter remain in Russia teaching and conducting scientific investigations. A younger daughter is a university student.

Among Professor Samoiloff's contributions to electrocardiography are the following papers:

Elektrokardiogrammstudien, Beitr. z. Physiol. u. Pathol. (Otto Weiss), 1908.

Elektrokardiogramme, Samml. anat. u. physiol., Vorträge u. Aufsätze (Gaupp and Nagel), Jena, 1909.

Praktische Notizen zur Handhabung des Saitengalvanometers und zur photographischen Registration seiner Ausschläge, Arch. f. Anat. u. Physiol. 478, 1910.

Weitere Beiträge zur Elektrophysiologie des Herzens, Arch. f. d. ges. Physiol. 135: 417, 1910.

Vorzüge der mehrfachen Ableitung der Herzströme bei Elektrokardiogrammaufnahmen illustriert an zwei Beispielen, Arch. f. d. ges. Physiol. 153: 196, 1913.

Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralstenose, (With Steshinsky, M.) München. med. Wehnschr. 56: 1942, 1909.

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#### JEAN HEITZ, 1876-1930.

A little more than a year ago Jean Heitz died in Seville, following a brief acute infectious illness while on a visit to Spain to conduct conferences before the medical faculty in Madrid and in San Sebastian and Barcelona. His death came as a shock to his friends and associates who had expected him to have many more years of active work in study and practice. He had edited the French heart journal—*Archives des maladies du coeur, des vaisseaux, et du sang*—from the date of its creation in 1907 to his death, carrying it on even during the Great War while he was at the front.



Born in Paris in 1876, the grandson of a physician, Heitz was a brilliant scholar even in his early childhood. In 1895 he studied medicine under Hayem, Netter, and Seglas and completed his medical training under Landrieux, Michaux, Dejerine, Merklen, Bezançon, and Babinski. It was in the service of his master, Pierre Merklen, that his interest in cardiology began, and that his idea came to create a physiotherapeutic establishment in France for patients with heart disease.

In 1903 he published his inaugural thesis "*Les nerfs du coeur des tabétiques*" for which he was awarded a silver medal. That same year he was named laureate of the faculty of medicine and installed himself at Royat after a visit to study the organization of the baths at Nauheim. Royat under the direction of Jean Heitz became the French health resort for patients with hypertension, and there Heitz carried on clinical investigations on hypertension and other aspects of circulatory disease. In 1907, as noted above, he became editor of the newly founded *Archives des maladies du coeur*.

From 1914 to 1919 he took an active part in the French military medical service, carrying on in connection with this service investigations on arterial lesions with Babinski, Labbé, and Letulle. It is for his work on arterial obliteration that he received the Bourceret Prize in 1926. Soon after the war, in July, 1919, he received the cross of the Legion of Honor.

From 1919 until his death in 1930 Heitz spent most of his time at Royat but studied in Paris during the winter months. He served as president of the Medical Society of Royat during the years 1927 and 1928 and in 1929 became president of the Society of Hydrology of France.

Not only in medicine was Heitz an able student and contributor but also in literature and art. Articles from his pen on Stendahl and Balzac were much appreciated in literary circles, and he took great delight in gathering together a fine library.

In writing this brief review of the life of Jean Heitz I wish to testify to the charm of his character, to the warmth of his hospitality during the war and afterwards, and to his great kindness in affording opportunities of seeing some of the heart work in France and of studying rare volumes in his fine library.

Paul D. White

# Department of Reviews and Abstracts

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## Selected Abstracts

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Seegal, David, Seegal, Beatrice Carrier, and Jost, Elizabeth L.: Local Anaphylactic Inflammation in the Rabbit Pericardium, Heart and Aorta. *J. Exper. Med.* 55: 155, 1932.

An intense inflammatory reaction in the pericardium, heart and intrapericardial aorta can regularly be produced in a sensitized rabbit by the intrapericardial injection of homologous antigen. The appearance of this reaction in sensitized animals is a manifestation of the Arthus phenomenon. The appropriate union of antigen and antibody in such an area as the pericardial cavity leads to striking changes. Gross changes were present in thirteen of the seventeen sensitized animals studied. The lesions of "spontaneous interstitial myocarditis" could be found after careful study in about one-half of these animals.

The authors believe that a possible explanation for the development of the myocarditis in these animals may be found in previous work which showed that such a substance as trypan blue would extend back through the rabbit heart after intrapericardial injection. They believe that the diffusible antigen in the present experiments might pass through the myocardium and produce the changes noted in the heart.

Griep, Leo H.: Electrocardiographic Studies of the Effect of Anaphylaxis on the Cardiac Mechanism. *Arch. Int. Med.* 48: 1098, 1931.

Electrocardiographic changes in the guinea pig are analogous in artificial asphyxia and anaphylaxis. The changes consist of bradycardia, partial and complete block, inversion of the T-wave, with a shortened R-T interval and a high T-wave take-off and auricular and ventricular fibrillation. The changes in the T-wave are not unlike those noted in coronary occlusion and suggest the possibility that disturbances in the cardiac mechanism may be due to myocardial anoxemia. The foregoing conclusions are also true of the rabbit during asphyxia, during anaphylaxis and in a condition following clamping of the pulmonary artery.

Microscopic sections of the hearts of guinea pigs and rabbits revealed nothing of note as a physical basis for the changes observed. The vagus nerve does not seem to play an important rôle in the production of the disturbances in mechanism. The functional cardiac changes observed in the guinea pig and rabbit during anaphylaxis are not specifically due to the anaphylactic state but rather to the state of asphyxia that anaphylaxis induces.

Tuohy, E. L., and Eckman, P. F.: Aortic Stenosis With Calcareous Nodules in the Aortic Valves. *Minn. Med.* 14: 289, 1931.

Post-mortem findings in three patients are presented. These findings consisted of greatly enlarged hearts with isolated changes in the aortic cusps inducing high grade aortic stenosis. Associated with these changes was constantly found an associated (secondary) aortic insufficiency. Three other cases without postmortem examination

also are included in the report. The same findings on physical examination have been observed, and a probable diagnosis of a similar change in the aortic valve has been made.

The distortion in the aortic cusp was found to be due to nodular calcium deposits. The manner of the deposition of this material is discussed. This lesion and the resulting syndrome may account for typical attacks of angina pectoris in which the coronary vessels have shown no change.

In these patients there has been an absence of rheumatic history, and the other valves in the heart were found to be normal.

The degree of enlargement of the left ventricle to be found in patients with aortic stenosis should lead one to investigate such very large hearts for evidence of calcareous nodular deposits in the aortic cusps. Importance and value of careful attention to heart outlines and in clinical cases to presumptive weights are discussed.

Coombs, Carey F.: *The Work of the University Centre of Cardiac Research.* Bristol Med-Chir. J. 48: 179, 1931.

The scope of the work together with some of the results obtained in the past four years at the Cardiac Centre are described in this brief report. The following facts have been observed and are worthy of note. During the three years under review, Bristol's population of about 400,000 included 750 children with rheumatic heart disease, while the surrounding country with about 1,100,000 inhabitants had 350 of these children, the incidence in the city being six times as high as in the country. Observations have shown that the infective agent enters the cardiac tissue by way of the coronary blood supply, as shown by the damage occurring in a majority of cases in the arteries and at the root of the aorta. One paper on abdominal manifestations supports the view that the peritoneum is occasionally attacked by a rheumatic infection.

It is believed that ulcerative endocarditis is for the most part a terminal infection. It is believed that in cardioaortic syphilis, apart from gummata which are rarely seen in the heart, the present lesion is an aortitis which injures the heart not only directly by depriving it of the health it is entitled to expect from the aortic elasticity but also by infiltrating the bases of the aortic cusps which are thereby rendered incompetent and by narrowing the mouths of the coronary arteries and thus starving the myocardium. The virus whether spirochete or toxin or both is brought to the aortic wall by the lymphatics which surround it.

Leary, Timothy: *Early Lesions of Rheumatic Endocarditis.* Arch. Path. 13: 1, 1932.

As county medical examiner, the author was able to study the early phases of rheumatic endocarditis in persons who came to violent deaths while in apparent full health, or who died suddenly without hospitalization and on whose cardiac valves were found the early lesions of rheumatic endocarditis. The principal material was obtained from three patients: the earliest phase from an apparently healthy boy of six years, whose death was due to violence, with an endocardial lesion of the mitral valve before verruca formation; an intermediate phase from a girl of eighteen years, who had mitral stenosis for eight years before her death, with the endocardial lesion on the tricuspid valve, associated with verruca formation in various stages; a late phase from a man, aged fifty-one years, who had an old but not advanced mitral process, with the lesion on the mitral valve and showing pseudoverrucae due to thrombus formation.

There was found an unusual tissue reaction, in the form of a cell palisade along the contact edges of the cardiac valves, which appears to be a specific response of

allergic tissue to an infection. The absence of an acute inflammatory reaction in the tissue of the valve and the apparent efficiency of the defense afforded to the underlying tissue in the presence of infecting organisms on the surface are striking.

It is believed that the formation of the cell palisade and the production of verrucae result from injury to the surface of the valve and not from injury arising within the valve. The evolution of the verrucae from local regions of damage of the defensive palisade is described.

Shookhoff, Charles, Litvak, Abraham M., and Matusoff, Irving: Paroxysmal Tachycardia in Children. *Am. J. Dis. Child.* 43: 93, 1932.

Four cases of paroxysmal tachycardia in children are reported. Three of the cases showed paroxysmal auricular flutter and one paroxysmal tachycardia. The latter case showed evidence of severe rheumatic myocarditis and endocarditis, of which the occurrence of the paroxysmal tachycardia was one of the early symptoms if not the first symptom.

The authors are inclined to believe that the occurrence of these disturbances of mechanism are due to disease of the myocardium and that they have considerable importance in the prognosis of these cases. While such children may live for many years, it would seem that the association with myocarditis would shorten their expected duration of life. The differential diagnosis between paroxysmal auricular flutter and other types of paroxysmal tachycardia is discussed.

Morse, John Lovett: The Prognosis of Acute Endocarditis in Childhood. An Analysis of One Hundred Cases. *Am. J. Dis. Child.* 42: 735, 1931.

Of 100 children seen during the first attack of acute endocarditis from ten to thirty years before this article was written, 36 are dead, 3 are cardiac invalids, 61 are alive and well. Thirty-seven of those who are alive and well have normal hearts, 18 have slightly damaged hearts, and the hearts of 6 were not examined. The age at the time of the onset of the disease and the intervals elapsing between the onset and the time when the patients were first seen had no apparent influence on the prognosis. In the cases in which rheumatism seemed to be the cause, the results were not so good as in those in which the apparent cause was an infection of the upper respiratory tract. Myocarditis and pericarditis were unfavorable signs. Recurrences of the rheumatic infections were not as common as is usually believed, and repeated attacks did not always prevent recovery. Only one of the patients who are alive and well has a diastolic mitral murmur.

Tallerman, K. H.: Abdominal Manifestations in Rheumatism. *Brit. M. J.* 2: 844, 1931.

In view of the frequency with which rheumatism occurs in children of the hospital class and the number of times one is confronted with a child suffering from abdominal pain without other signs or symptoms, it is worth while considering how often children with these abdominal symptoms may be actually suffering from rheumatism of which this pain is at the time the only manifestation.

Two cases are reported which give findings suggestive of this situation. It is felt that cases similar to those described probably occur more frequently than is generally recognized.

Weiss, Morris M.: The Electrocardiogram in Children with Chronic Rheumatic Heart Disease and Heart Failure. *Am. J. Dis. Child.* 42: 1339, 1931.

An analysis was made of the electrocardiograms of eighty-seven afebrile children with chronic rheumatic heart disease and regular sinus rhythm. The average height

and duration of the P-wave were greater than normal in all leads, owing to the predominance of cases of mitral stenosis and insufficiency. Notching of the P-deflection was frequently associated with the cases of mitral stenosis and those showing decreased functional activity. Notching was also associated with tall and long P-waves. The auriculoventricular conduction time was increased in 30 per cent of the cases. No other disturbances in intraventricular conduction were noted.

Spontaneous variations in the T-wave which were found to occur when daily records were taken must be considered when digitalis studies are made in children.

Right axis deviation was found in 60 per cent of the patients with mitral stenosis.

It is felt that routine electrocardiograms had only a confirmatory diagnostic value. An abnormal electrocardiogram had a definite prognostic importance since the largest and longest P-waves and those records that showed notching of the peak in all leads occurred with the greatest frequency in the groups of children suffering with advanced heart failure.

**Seham, Max, Shapiro, M. J., and Hilbert, Eunice H.: The Early Diagnosis of Rheumatic Heart Disease in Children. Am. J. Dis. Child. 42: 503, 1931.**

In 809 patients admitted to the Lymanhurst Cardiac Clinic during a period of seven years, 46 per cent of the cases were diagnosed as organic heart disease and 54 per cent as no heart disease. Of 379 cases of organic heart disease, 18 per cent were congenital lesions of the heart, 74 per cent were rheumatic in origin, only 3.6 per cent were due to other causes, and 4.4 per cent were undiagnosed. According to the statistics in this study, the most reliable means of diagnosis is the history. A questionnaire used in the study gives more positive data than informal questioning. In 92 per cent of the cases of early mitral disease, it was possible to obtain a history of rheumatism according to the definition used.

The problem of differential diagnosis revolves chiefly around the children who present the following conditions: (1) a systolic murmur with or without circulatory signs and symptoms, (2) rheumatism and a systolic murmur that has escaped carditis, (3) rheumatism and a systolic murmur that ultimately develops into chronic endocarditis, and (4) congenital heart disease, especially patency.

Various methods of examination and functional tests of heart efficiency are discussed. The authors have used esophagrams and have developed a cardi thoracic index. They believe that so-called functional heart tests are of no value in determining the myocardial efficiency of the heart.

**Shookhoff, Charles, and Taran, Leo M.: Electrocardiographic Studies in Infectious Diseases. II. Scarlet Fever. Am. J. Dis. Child. 42: 554, 1931.**

Fifty hospital patients with scarlet fever admitted consecutively were studied. The observations showed that there is a comparative infrequency of electrocardiographic evidence of myocardial involvement, that there was no tendency for abnormalities when present to persist and that there was no prolongation of the P-R interval.

**Sutton, Lucy Porter: The Treatment of Chorea by the Induction of Fever. J. A. M. A. 97: 299, 1931.**

Twenty-four cases of chorea have been treated with intravenous injections of typhoid paratyphoid vaccine as a means of producing protein shock fever. There has been prompt cessation of the symptoms, and the course of the disease in these patients has seemed to be greatly shortened. In the cases reported, the average duration after treatment was started was from eight to nine days. A comparison has been made of children treated by this form of therapy with those treated by phenyl ethyl

hydantoin. The protein shock fever appears to have definite advantages over drug therapy. The procedure for the treatment is outlined in this article.

Waggoner, R. W.: Sydenham's Chorea. *Am. J. M. Sc.* 182: 467, 1931.

The author has made a study of chorea occurring in a series of 125 patients. The incidence was twice as high in females as in males and was noted to occur chiefly between the ages of five and fifteen years. In addition to the characteristic movements, it was noted that the disease was practically almost always associated with mental symptoms during the acute stage. It is pointed out that these variations of normal personality reactions may have been accentuated rather markedly by ill-advised handling and treatment particularly in the home before the diagnosis was recognized. It was also observed that the disease most likely occurs in individuals in whom there is a predisposition which is the result or the cause of a poor integration of the cerebrocerebellar motor mechanism. Pathologically it is a type of encephalitis characterized by involvement of both the cortex and the basal ganglia but particularly of the corpus striatum and perhaps the corpus Luys.

The most essential part of the treatment of chorea is absolute mental and physical rest, best obtained by the removal of the patient from his home and placing him in an institution where his environment can be properly controlled. The multiplicity of treatments suggested are evidence of their inadequacy. The removal of the foci of infection is important but should be delayed until the child has become accustomed to his new environment, until there has been a diminution in the movements exhibited and until the fever which the patient may have has disappeared.

Weiss, Harry, and Ottenberg, Reuben: Relation Between Bacteria and Temperature in Subacute Bacterial Endocarditis. *J. Infect. Dis.* 50: 61, 1932.

The results of a study of the relationship of the temperature to the bacteremia in four cases of subacute bacterial endocarditis indicate that a correlation between these two phenomena probably exists. The phenomena are apparently maintained by a constant, practically uniform feeding of bacteria into the blood stream from the endocardial vegetations and again by the sudden liberation of a large number of organisms into the circulation producing the phenomenon of bacterial showers.

The constancy of the level of the bacteremia is a rather remarkable feature; each case apparently establishing for itself the balance between bacterial invasion and immunologic response which is maintained throughout the course of the disease.

The studies indicate that higher bacterial counts in blood cultures would be obtained if the cultures were made during the periods of low temperature just previous to the expected rise.

Gwyn, Norman B.: Subacute Meningococcal Endocarditis. *Arch. Int. Med.* 48: 1110, 1931.

A case is reported that for eight months showed symptoms and physical signs which one is accustomed to associate with infection of the heart valves by *Streptococcus viridans*—subacute bacterial endocarditis. Blood cultures in the last two weeks of the illness were positive for meningococci. Death took place as a result of invasion of the brain and spinal cord by the meningococci.

The observations at autopsy agreed closely with those described as occurring in association with subacute bacterial endocarditis. Meningococci were recovered at autopsy from the meninges only. The lesions in the heart and kidney as described were apparently in accordance with those observations recorded at autopsy in cases of subacute streptococcal endocarditis.

Fulton, Marshall N., and Levine, Samuel A.: Subacute Bacterial Endocarditis, With Special Reference to the Valvular Lesions and Previous History. *Am. J. M. Sc.* 183: 60, 1932.

A clinical study has been made of 111 cases of subacute bacterial endocarditis; 30 of these were examined at post-mortem. Only 7 per cent of these cases showed definite clinical evidence of mitral stenosis and 13 per cent of those examined at post-mortem had mitral stenosis. There were 23 instances of mitral insufficiency and 66 of aortic and mitral insufficiency, 10 of which had signs of aortic stenosis as well. There were 5 with congenital abnormalities of the heart, and the remainder consisted of small heterogeneous groups. It is important to note that in spite of the great frequency of mitral stenosis as a type of chronic valvular disease, it was found to be associated comparatively rarely with subacute bacterial endocarditis.

The following general rules in regard to the interpretation of murmurs seem apparent from this study; first, if no murmur whatsoever is heard over the heart, one can practically dismiss the diagnosis of bacterial endocarditis; second, if only a systolic murmur is heard, the vegetations will be found limited to the mitral valve and adjacent endocardium (this excludes the rare cases of congenital heart disease); third, if there is in addition to a systolic murmur a basal diastolic murmur, one may predict that there are vegetations on the aortic valve and that there may or may not be a similar lesion on the mitral valve.

A previous history of some definite rheumatic infection was obtained in 51 instances. Forty-two had rheumatic fever, 3 had chorea and 6 had both. From an analysis of the degree and duration of rheumatic infection from which these patients suffered, they were found as a group to have been comparatively free from this type of infection for a considerable period of time preceding the development of subacute bacterial endocarditis. Twenty-eight of the 42 patients who had had rheumatic fever had had only a single attack. In these there was an average interval of 17.5 years before subacute bacterial endocarditis developed. It seems that immunity to rheumatic infection revealed in these patients renders them more susceptible to subacute bacterial endocarditis.

The study of the past history of these patients from the point of view of ability to work and of circulatory efficiency showed that the cardiac condition could be regarded as excellent in 76, good in 17, and fair in 10. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis; though there was satisfactory evidence that in 60 cases heart murmurs had been present for a period of years. It is believed that these patients, had they been examined shortly before the development of subacute bacterial endocarditis, would in most instances have shown a murmur.

The following other findings of interest have been recorded in this study. The males outnumbered the females 3 to 2. The average age of the males (35.7) was nine years greater than that of the females (26.9). The average heart weight in the autopsied cases was 489 gm. Significant arrhythmias were rarely found. Only 1 case showed auricular fibrillation and that was a terminal event. The average blood pressure in 92 patients on whom readings were obtained was 118 systolic and 52 diastolic. There were only 4 patients with a systolic pressure over 150 (all of whom had aortic insufficiency) indicating that hypertension is extremely rare in this form of heart disease. There were cases with very peculiar types of onset in which the evaluation of a systolic murmur was a most important clue to the diagnosis.

The patient who is most liable to develop subacute bacterial endocarditis is one who has had a mitral systolic or an aortic diastolic murmur for some years. If he gives a history of previous rheumatic infection, as happens in about half the cases, it is most likely to be a single attack with unusual freedom from recurrences. He

has been able to carry on essentially normal activities, has shown at no time any important irregularities of the heart or evidence of congestive heart failure and has either a low or a normal blood pressure.

**Lambert, Alexander: Cardiac Pain and Sudden Death.** *Am. J. M. Sc.* 182: 769, 1931.

In this comprehensive analysis of the subject, the author presents the many causes of sudden death. It is pointed out that the most frequent cause is not cerebral hemorrhage, but some cardiac lesion. It is also observed that sudden death is not of common occurrence in heart disease when all forms of heart disease are considered. A discussion of the cause of cardiac pain is presented together with a possible explanation. It is pointed out that stretching and overdistention of the first part of the aorta and of the coronary arteries are brought about by normal circulatory reflexes which in diseased tissues cause excessive stretching of the aorta before the depressor reflexes bring relief or by overfilling cause over distention of arteriosclerotic walls of the coronary arteries. As long as the circulatory reflexes do not upset the equilibrium between the myocardium and its blood vessels, there is no pain. When, however, the afferent functions of the nerves are adequately disturbed or the myocardium has degenerated so that it cannot under reflex stimulation contract normally, the normal increased rise of blood pressure and the circulatory reflexes produce excessive dilatation of the diseased blood vessels, and pain results when the heart endeavors to answer the demands for increased work.

**Brooks, Harlow: Concerning Certain Phases of Angina Pectoris Based on a Study of 350 Cases.** *Am. J. M. Sc.* 182: 784, 1931.

Observations made on a series of 350 cases of angina pectoris conform to those usually recorded by other writers. A discussion of the etiology and the pathological change in the heart and great vessels is included. Diagnosis and various forms of treatment of this condition are also presented.

**Robey, William H.: Cardiology, Old and New.** *New England J. Med.* 205: 992, 1931.

This delightful review of the advances made in the study of diseases of the heart is refreshing to one who chooses at times to pause and consider what advances have been made as the result of the intensive effort directed to the care and prevention of heart disease. The change in conception of various conditions, such as rheumatic fever, tonsils and syphilis, shows how much has been learned during the steady progress of the last few decades. While undoubtedly much remains yet to be accomplished, it is still apparent from such a review that progress is being made. Present conceptions of these various questions are carefully and clearly analyzed in this review.

**Schwartz, Sidney P., and Levy, Joseph: Digitalis Studies on Children With Heart Disease. IV. The Effects of Digitalis on the Edema of Children With Rheumatic Fever and Chronic Valvular Heart Disease in the Presence of Sinus Rhythm.** *Am. J. Dis. Child.* 42: 1349, 1931.

Sixty-seven children between the ages of four and fifteen years with congestive heart failure and rheumatic heart disease were given variable dosages of digitalis of a potency of 1 cat unit per cubic centimeter to the point of nausea and vomiting and for longer periods when these minor toxic signs did not appear.



All of these children were in the afebrile stage of the disease when these observations were made, and they all had a regular sinus rhythm with a ventricular rate that averaged from a minimum of 66 to a maximum of 110 beats per minute. In approximately one-third of the cases, the experiments were repeated on several occasions at a time when the children had shown increasing signs of congestive heart failure, such as swelling of the face and the abdomen, hydrothorax, ascites and edema of the legs with enlargement of the liver.

A loss of body weight within one week following the use of the drug, with striking improvement in the signs and symptoms, was observed in only one child among the sixty-seven. Even in this case it was not certain that the improvement resulted from the use of the drug. No therapeutic response to digitalis was noted in the other cases.

It is probable that the type and pattern of congestive heart failure following rheumatic fever and chronic rheumatic valvular heart disease are responsible for the refractoriness of these children to digitalis in effective doses.

**Wolferth, Charles C., and Wood, Francis Clark:** The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads. *Am. J. M. Sc.* 183: 30, 1932.

Many cases of coronary occlusion do not show characteristic changes in routine electrocardiograms. It seems that there are "silent areas" in the heart where infarction may occur without producing a deviation of the S-T interval from the isoelectric line in any of the three conventional leads. The authors found that typical electrocardiographic evidence of cardiac infarction in experimental animals could be recorded by applying the electrodes to the anterior and posterior surfaces of the chest wall. After occlusion of arteries supplying hitherto silent areas, it was possible to determine striking deviations in the S-T interval. These results make it apparent that the anteroposterior chest lead (Lead IV) is an important adjunct to the routine electrocardiogram in the diagnosis of certain cases of coronary occlusion.

Two cases are reported to illustrate the use of this Lead IV. In the first, eight days after the original infarction, there was striking and unmistakable deviation of the S-T interval in Lead IV. In Case II, both Leads I and IV showed evidence of coronary occlusion, Lead IV showing a much more striking S-T interval deviation than that seen in Lead III.

**Schultz, Mark P.:** The Use of Amidopyrine in Rheumatic Fever. *Arch. Int. Med.* 48: 1138, 1931.

In the treatment of patients with rheumatic fever in the Hospital of the Rockefeller Institute, it has been found that amidopyrine is decidedly superior to other drugs heretofore employed; namely, sodium salicylate, acetylsalicylic acid, the ethyl ester of phenylcinchoninic acid, cinchophen and neocinchophen. Brief review of the literature concerning it is presented as a preliminary to the account of the observations presented in this paper on rheumatic fever.

Experience indicates that amidopyrine may be employed in daily doses of at least three grams without provoking symptoms of toxicity. Instances of idiosyncrasy are less frequent than with any other drug of this type. In rheumatic fever it has been found effective in patients not relieved by other drugs or unable to tolerate them in the therapeutic doses; and total daily doses of less than two grams have been found adequate in this disease. The feasibility of giving effective quantities without provoking untoward side actions, as well as the wide margin between therapeutic and toxic doses, renders this drug particularly valuable in the treatment of patients with rheumatic fever.

McEachern, Donald, and Baker, Benjamin M.: Auricular Fibrillation. Its Etiology, Age Incidence and Production by Digitalis Therapy. *Am. J. M. Sc.* 183: 35, 1932.

A study has been made of the records of 575 patients seen during the past twelve years in whom the electrocardiograms have at one time or another shown auricular fibrillation.

The etiological relationships to the various forms of cardiac disease are tabulated. The infrequent occurrence of the arrhythmia in the first decade of life is described and two additional instances are recorded. Emphasis is laid upon the rarity of auricular fibrillation in syphilitic cardiovascular disease.

In the present series, 35 per cent of the cases were associated with rheumatic heart disease and only 3 per cent with syphilitic cardiovascular disease. Note is made of the production of auricular fibrillation by administration of digitalis.

Stroud, William D., LaPlace, Louis B., and Reisinger, John A.: The Etiology, Prognosis and Treatment of Auricular Fibrillation. *Am. J. M. Sc.* 183: 48, 1932.

The present series consists of 253 cases of chronic fibrillators, those having paroxysmal fibrillation or in whom normal sinus rhythm returned spontaneously having been eliminated. The cases have been followed over a period of at least one to eighteen years after the onset of fibrillation. Diagnosis has been confirmed by electrocardiograms in each case.

Throughout the series no common etiologic factors have become apparent. The presence of auricular fibrillation does not necessarily imply a worse prognosis than in the nonfibrillating heart with an equal amount of cardiovascular damage.

The average age of onset of auricular fibrillation due to rheumatic cardiovascular damage was thirty-nine years. The prognosis is very poor in such patients developing fibrillation before the age of twenty-five. Of 65 patients with manifestations of rheumatic cardiovascular disease before the age of twenty-five, 86 per cent had developed auricular fibrillation before the age of forty and 88 per cent had died before the age of fifty-three years. The average age of onset of auricular fibrillation in the arteriosclerotic (nonrheumatic) group is about fifty-nine years. Of the eighty-eight cases, none had begun to fibrillate before the age of forty years, and 72 per cent developed auricular fibrillation after the age of fifty-three years. Fibrillation associated with thyrotoxicosis will usually terminate spontaneously following partial thyroidectomy and, if not, almost invariably will respond promptly to quinidin therapy after such an operation. Syphilitic cardiovascular disease is comparatively rarely associated with auricular fibrillation.

In the treatment of patients with auricular fibrillation, digitalis usually proves most satisfactory. It is only in the exceptional case that a restoration to normal sinus rhythm by quinidin sulphate is of more apparent value to the patient than the establishment of a daily maintenance dose of digitalis. Although there appears to be little danger of accident from the use of quinidin sulphate in properly selected cases of auricular fibrillation, yet the authors feel this drug should be used in those few cases of younger individuals with slight or no demonstrable cardiovascular abnormality except the arrhythmia or in thyrotoxic patients following partial thyroidectomy without a spontaneous return to normal sinus rhythm.

Campbell, S. B. Boyd, and Turkington, S. I.: Right Bundle-Branch Block. An Analysis of the Clinical Records of Fifty-Six Cases With Typical Electrocardiograms. *Quart. J. Med.* 24: 481, 1931.

The investigation of this series of fifty-six cases was undertaken with the object of reviewing the signs and symptoms associated with the condition and of obtaining

figures which might prove useful for prognosis. Thirty patients were in the hospital, and twenty-six had been seen in consultation practice. The incidence was roughly 1 per cent of the total patients seen in the same time. No characteristic etiological factor was found in the group. Thirty-six of the cases were men. The average age incidence was about sixty years. The symptoms and signs were those commonly found due to myocardial degeneration. In the hospital group, there was a case mortality of 73 per cent of the cases which could be traced. The second or nonhospital group showed a case mortality of 42 per cent.

Parkinson, John, and Cookson, Harold: The Size and Shape of the Heart in Goitre. Quart. J. Med. 24: 499, 1931.

A consecutive series of 130 patients with goiter causing symptoms was examined with the primary object of deciding the size and shape of the heart by radiography. In addition a series of post-mortem records of 43 goiter cases was investigated to determine the incidence and distribution of cardiac hypertrophy.

Of the forty-three cases of goiter all but three had shown the classical symptoms of thyroid intoxication. There proved to be hypertrophy of the heart in more than one-half. The increase involved both ventricles as a rule, sometimes the left more than the right, occasionally the left alone. A predominant or isolated hypertrophy of the right side was never seen. In general it was the younger patients and those with the shorter duration of symptoms who showed no hypertrophy. It was also in the younger patients, say under thirty years, that the rhythm had been normal throughout or fibrillation had come only as a terminal event.

Established fibrillation occurred in older people with an average age of twenty-one years in eight cases at death. The heart weight was greater on the average in those with established fibrillation than in those with normal rhythm. The greatest increase in heart weight was registered in those with fibrillation and heart failure. When emaciation was extreme, the heart was only slightly or not at all hypertrophied. In the three cases of goiter where the gland had not been suspected of producing symptoms, there was cardiac hypertrophy in two, and perhaps in the third.

Clinical and x-ray observations were made on 130 patients with goiter and symptoms from it. Without x-ray examination it is difficult to determine the size of the heart, especially when there is tachycardia, and either a teleradiogram or an orthodiagram or both were taken of every patient. The criteria of enlargement applied to these records are discussed. Enlargement was found in about 45 per cent of cases, usually slight or quite moderate, but not rarely great. In most it involved both contours of the heart, but more particularly the left and sometimes the left only. Although several cases with striking displacement and some stenosis of the trachea were included, enlargement of the right side of the heart alone was never seen. Electrocardiograms, so far as they can be used as an indication of hypertrophy and its relative distribution, confirmed the radiographic and post-mortem findings.

The incidence of auricular fibrillation, including both paroxysmal and established forms, was 27 per cent. Heart failure was present at some time in twelve, and all these had fibrillation, except one with a complicating hypertension.

A few serial records showing progressive increase in the heart size were obtained, all from patients with permanent fibrillation. Comparison between records taken before and after thyroidectomy was made in eleven cases and gave variable results: there might be no change, an increase, or a decrease in the transverse diameter of the heart. After operation several factors come into play which render it difficult to accept the changes as evidence of actual alteration in heart size.

The form of the heart is often affected in a characteristic way in goiter. Undue prominence of the pulmonary arc was a striking feature of about one-third of the

series, sometimes appearing as a convexity on the left profile, sometimes combining with an enlargement of the heart to the left to render this profile straight. An exaggeration of this arc is often an early change, preceding any enlargement of the heart chambers. Post-mortem measurements showed that the pulmonary artery was often dilated.

The left auricle was not enlarged out of proportion to that of other chambers of the heart—a sharp distinction from the heart of mitral stenosis. The superior vena cava was sometimes prominent; this would be expected with the venous congestion of heart failure, but such an explanation only applied to a small proportion. The aortic arch reached too high a level in the chest in about one-third. The form of the vascular pedicle was modified occasionally by a retrosternal goiter.

When symptoms are mild or of short duration, the heart in goiter is normal in size and shape. When symptoms are severe and of long standing, it is in a fair proportion both enlarged and modified in shape. The greatest enlargement is seen with auricular fibrillation and failure. The special form characteristic of the goiter heart is based upon a combination of prominence of the pulmonary arc, of the left ventricle, and to a minor extent of the right auricle. As a result of these changes, the heart may be generally enlarged, the contour retaining much the same shape as in the normal heart; whereas almost all other forms of cardiac disease causing enlargement greatly modify the shape. In their fully developed form changes in the left arc produce a distinctive picture with its straight left border and a right auricular arc only slightly enlarged. The heart so disposed, when seen from in front, has some resemblance to a ham. This picture differs from that of mitral stenosis in the relatively slight prominence of the right auricle and the fuller aortic knuckle as seen from the front and in the absence of left auricular enlargement as seen in the first oblique position. It approximates more the cardiac outline of combined mitral stenosis and aortic incompetence.

Radiological examination is a help in judging the presence or severity of a cardiac lesion in a patient with goiter.

The demonstration of cardiac enlargement is important from the standpoint of the surgical treatment of goiter. When present, it is an added reason for, rather than a contraindication to, surgical treatment. Though the greater the enlargement, the poorer is the prospect of a complete return to normal, yet the aid of surgery will often be required to check the progress of the lesion.

In deciding the cause of obscure cardiac symptoms or enlargement, or of auricular fibrillation with or without failure, the discovery of the characteristic radiographic picture may suggest a goitrous etiology.

Harrison, T. R., Calhoun, J. Alfred, and Turley, F. C.: Congestive Heart Failure.

XI. The Effect of Digitalis on the Dyspnea and on the Ventilation of Ambulatory Patients With Regular Cardiac Rhythm. *Arch. Int. Med.* 48: 1203, 1931.

The effect of digitalis has been studied in forty-three patients with regular cardiac rhythm. Most of the patients had never had congestive failure. None of them had more than slight edema at the time they were studied and the majority had none. The following results were obtained: Nineteen patients had paroxysmal nocturnal dyspnea. Sixteen of these persons were completely relieved and one was worse after the drug. Forty-three patients had dyspnea brought on by exertion. Definite benefit was obtained in fifteen of these, apparent benefit in fourteen and no improvement in twelve, and two patients were worse after the drug. In eight subjects the vital capacity, ventilation per square meter on standardized exercise, and ventilation index were studied. Seven of the eight patients reported clinical improvement of some degree, and in all of them measurements of ventilation also indicated improvement.

One patient felt worse after digitalis, and objective study of the ventilation showed that he was worse.

As a result of this study, it is concluded that digitalis is of great benefit in patients with paroxysmal dyspnea and is of some value in many patients with dyspnea brought on by exertion.

The number of patients with rheumatic heart disease was too small to justify generalization in regard to this observation, but patients with hypertensive, arteriosclerotic and syphilitic heart disease were usually benefited.

The observations concerning the ventilation index seemed to indicate that this method of study may be of some general use in evaluating therapeutic measures in patients with cardiac disease. It has been possible to determine whether a given drug was of value in combating cardiac edema because the urine volume could be measured and the patient could be weighed. However, methods of expressing dyspnea quantitatively have not heretofore been available.

Harrison, T. R., Ashman, R., and Larson, R. M.: Congestive Heart Failure. XII. The Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart. *Arch. Int. Med.* 49: 151, 1932.

A study of ventricular fiber thickness, heart rate and the length of diastole has been made in a number of animals of different species, in normal human subjects of various ages and in human adults with enlarged hearts. It has been found that in all normal subjects a thick ventricular fiber is associated with a slow heart rate and a thin heart fiber with a fast heart rate. It is believed that the slow heart rate in animals with thick cardiac fibers is advantageous because the recovery period of the heart is prolonged. This prolonged period, for example, affords opportunity for the oxygen to diffuse through the thicker fiber.

It was found that subjects with enlarged hearts have heart rates much faster than would seem to be optimal for such thick fibers. These observations suggest that "cardiac fatigue" may be due in part to a heart rate which is faster than optimal. It is believed that this conception may explain why congestive heart failure may occur in the absence of any demonstrable myocardial abnormality other than hypertrophy and dilatation. It is suggested that a heart rate much slower than normal would be of great benefit to patients with hypertrophied hearts.

Macpherson, Walter E., Essex, Hiram E., and Mann, Frank C.: The Rate of Disappearance of Glycogen During Contraction of the Perfused Heart of the Rabbit. *Am. J. Physiol.* 99: 429, 1932.

Rabbits' hearts were analyzed for glycogen content. The hearts were cut into sections, and the glycogen was ascertained for various levels. A series was analyzed for control purposes, another series was perfused with Ringer-Locke solution, containing glucose, and a third series was perfused with the same type of solution but free of glucose. The methods of perfusing and sectioning the hearts and the results obtained are given.

It was found that the glycogen content of the rabbits' hearts varied at different levels; it is highest in the auricles, next highest at the apex, and gradually diminishes toward the base of the ventricles. More glycogen disappears in the first hour of perfusion than at any succeeding time. It was also noted that the ventricles of perfused rabbits' hearts continue to contract after large amounts of ventricular muscle are removed for study. The activity of such hearts apparently is not definitely shortened.

Patek, Arthur, and Weiss, Soma: *The Tonus of the Autonomic Nervous System in Arterial Hypertension*. *New England J. Med.* 205: 330, 1931.

The psychic state and the tonus of the autonomic nervous system of forty-two patients with essential hypertension were compared with that of thirty-seven control patients with a normal cardiovascular system. While no one symptom or sign used for the evaluation of the autonomic nervous system was absolute or pathognomonic, the following symptoms and signs, in combination, distinctively, were more frequently present in patients with essential hypertension than in control subjects: (1) overexcitability, impulsiveness, a tendency to worry; (2) a negative hippus; (3) absence of sinus arrhythmia; (4) negative or reverse oculocardiac reflex; (5) a persistent brittle third tone throughout six sphygmomanometer cuffings; (6) "white" dermatographic reaction both to light and to heavy pressure; (7) tendency to telangiectasis.

As judged from tests performed, the minute vessels of the skin in arterial hypertension are hyperirritable and have a tendency to react with pressor rather than with depressor responses.

A striking difference in the tonus of the autonomic nervous system in arterial hypertension as compared with that of controls does not exist. On the whole, however, the influence of the parasympathetic nervous system is less and of the sympathetic nervous system more pronounced in patients with arterial hypertension than in control subjects with a normal cardiovascular system.

de Vecchi, Bindo: *The Endocarditic Process in Childhood*. *Arch. Path.* 12: 49, 1931.

The author has analyzed the incidence of valvular endocarditis in children, using the postmortem material of the Institute of Pathological Anatomy of Florence, Italy, amounting to 4,952 autopsies in all. One hundred and seventy-nine cases of endocarditis are noted, ninety-three of which were acute and eighty-three subacute or recurrent. Tables accompanying the text indicate that the incidence of this process is infrequent in the first decade of life, there is a slight increase in the second and a material increase in the third decade in this series, amounting to about forty-three cases. From this point there is a gradual decline to old age.

The author describes the histologic changes occurring in the heart valves. He states that the diagnosis of endocarditis is not always possible with a histological examination and ought to be extended to all cases in which any active participation of valvular tissues can be demonstrated microscopically. This is particularly true in the early period of life. The valvular changes are regarded as the characteristic feature of the process while the thrombotic lesions are considered as merely secondary changes often absent throughout the course of the disease. The histologic changes are described in detail.

It is interesting to note the very infrequent occurrence of this condition in Florence. This infrequency would not coincide with observations in more northern countries, especially in the United States and England. It would be interesting to compare these autopsies with the incidence of heart disease in young children during the first decade of life attending clinics in the same community.

Ellis, Laurence B., and Weiss, Soma: *Studies in Complete Heart-Block*. 1. *The Cardiac Output and the Peripheral Circulatory Mechanism*. *Am. J. M. Sc.* 182: 195, 1931.

Two studies were made with five patients with complete heart-block; 2 of whom showed no, two moderate and one pronounced functional disability. The two

patients with no functional incapacity and no arteriosclerosis had normal arterial blood pressure, the remaining three had a systolic hypertension. In the absence of cardiac failure, the venous pressure was normal. Four patients had basal metabolic rates in the lower part of the normal range, the fifth had a metabolism 20 per cent below normal. In the four—patients with no circulatory failure at rest normal values for the cardiac output per minute were found. The cardiac output per beat in these patients were increased 40 to 50 per cent about normal. In the fifth patient with circulatory failure in bed, indirect evidence of a decreased blood flow was obtained. The circulating blood volume was reduced in each of four patients; it was not measured in the fifth. The circulation time was estimated by the histamine reaction method. The cardiac output was estimated according to the technic of Field, Bock, Gildea and Lathrop.

The increased stroke volume of the heart, the systolic hypertension, the reduced blood volume and possibly the somewhat lowered basal metabolic rate may be considered compensatory responses tending to maintain a constant and adequate blood supply to the tissues during the prolonged diastolic pause consequent upon the slow heart rate. The degree of elevation of the lactic acid and the changes of blood gases following exercise were normal in one patient who had good functional capacity.

The authors believe that complete heart-block is not incompatible with a normal life and that the prognosis as to health and life is much more dependent on the presence or absence of accompanying myocardial disease than on the block itself.

**Cole, Leslie:** Heart-Block Following Acute Appendicitis. *Lancet*, 1: 907, 1931.

Four days following an operation for an attack of acute appendicitis the patient developed irregular pulse which later became slow and which was diagnosed from frequent electrocardiograms as heart-block. No other cause for the disturbance of mechanism could be found. The patient recovered and on the twenty-sixth day the electrocardiogram was quite normal. The most likely explanation is that a mild bacteremia was associated with a subsiding local inflammation in the appendix region and caused a small focal inflammatory lesion in the region of the Bundle of His which interfered temporarily with conduction. Possibly, the pain in the right shoulder and the inflammation in the right conjunctiva may have been due to similar focal lesions.

**White, Paul D.:** The Treatment of Heart Disease Other Than By Drugs. *Jour. Am. Med. Assn.*, lxxxix, 436.

In the treatment of heart disease the most important relief frequently comes from agents other than drugs. Rest and recreation, physical and mental; exercise, climate, psychotherapy, physical therapy, regulation of the diet, and of the fluid ingested, surgical intervention and venesection all have a place of variable importance in the therapy of acute and chronic heart disease.

The author points out with particular care the relationship that must be maintained between physician and patient. He points out that often times the physician must in his judgment vary his methods to suit the particular circumstances which exist in the individual patient. Ofttimes hard and fast rules cannot be laid down.

Parkinson, John, and Beford, D. Evan: Cardiac Infarction and Coronary Thrombosis. *Lancet*, 1928, i, 4.

The present paper is based on the clinical study of 100 patients who had experienced one or more prolonged severe attacks of anginal pain and in whom no diagnosis other than myocardial infarction seemed possible. Doubtful cases and those of post-mortem interest only have been excluded. A supplementary study has been made from the records of the Pathological Institute of the London Hospital from 1922 to 1926 for comparison. Altogether 83 such cases are included. The various data concerning cardiac infarction and thrombosis are analyzed in detail. The high incidence of males affected, the suddenness of the onset and the association with sudden death coincide with the figures gained from other similar studies. The authors describe the various usual and special clinical features. They believe that as a rule the electrocardiogram after cardiac infarction is characteristic and occasionally it provides the only objective sign of such a cardiac lesion. The diagnostic feature is the absence of an isoelectric period between the RS- and T-waves, so that a plateau type of curve results in which the R-T interval is either elevated or depressed.

Berman, P., and Mason, V. R.: Coronary Artery Disease and Electrocardiographic Study. *Calif. and Western Med.*, 1928, xxviii, 334.

The authors consider the changes in the electrocardiogram described by Pardee as being specific in the diagnosis of coronary thrombosis. They describe this as a downward sharply peaked T-wave with an upward convexity of the S-T or R-T interval in all or any leads except Lead III. When this type of curve occurs in Lead III with other signs of myocardial damage, it may be of importance. The authors have studied electrocardiograms showing these changes in relation to the clinical course shown by patients in four groups.

Group one includes patients in whom a diagnosis of coronary occlusion made by clinical and electrocardiographic methods was confirmed by post-mortem findings. In an equal period of time there were in the hospital 13 patients who had no electrocardiograms made, but showed occlusion of the coronary artery at autopsy. No clinical diagnosis of the condition had been made in this group.

In a second group, including 18 patients, there were symptoms of coronary thrombosis with characteristic electrocardiograms, but in whom there were no autopsies. The electrocardiograms showed other signs of myocardial injury and the patients had clinical signs to coincide with these findings.

Group three includes 9 patients all with syphilitic heart disease. These all showed characteristic coronary T-wave changes.

Group four included 19 patients with characteristic coronary T-wave changes in the electrocardiogram but in whom no clinical diagnosis of occlusion could be made. None of these patients had come to autopsy.

The authors feel that the occurrence of such changes in the electrocardiogram are of value in the diagnosis of coronary thrombosis.

Sprague, Howard B., and White, Paul D.: Auricular Flutter. *Jour. Am. Med. Assn.*, 1928, xc, 1772.

In a man aged forty-nine auricular flutter was diagnosed from the history and by electrocardiogram. The condition had existed apparently for five years



and was unchecked by digitalis or quinidine in full dosage. No cause for the disturbance in mechanism could be found nor was there any evidence of heart disease. The flutter finally stopped abruptly for no known reason. Not infrequently during the course of the flutter, the ventricular rate followed the auricular, without block, at from 240 to 260 beats a minute. At such times palpitation and weakness were distressing.

## Book Reviews

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VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Edited by Doctor Bruno Kisch. Dresden und Leipzig, 1931, Theodore Steinkopff.

These transactions, which record the work of the fourth annual meeting of the German Association for the Study of the Circulation, make up a substantial volume of about 250 pages, which contains some thirty papers and critical reviews dealing with various aspects of cardiovascular disease. About one-half of these are concerned with the chief topic of the meeting—digitalis. Almost every phase of the pharmacology and therapeutics of the digitalis bodies is considered, and one is impressed with the scientific character and high quality of most of the articles. The list of contributors includes a good many well-known names and testifies to the standing of the Association and the quality of its output.

*L. A. C.*

THE CARDIAC CYCLE by Harrington Sainsbury. New York, 1931, 79 pp., William Wood and Company.

The purpose of this little book, as set forth in the introductory chapter, is to detail the events of the cardiac cycle and to relate them to blood movement and the pulse. The author conveys the impression at the outset, by introducing Newton's laws of motion and emphasizing the application of these principles to cardiodynamics, that he proposes to make the book essentially physical in its point of view.

A discussion of auricular and ventricular systole presents to the reader the notions (1) that the auricle projects its contents into the ventricle and thereby gives rise to a stretching of, and an impact wave in, the ventricle, and (2) that ventricular systole arises in the thin portions of the apex—a fortunate provision of nature to obviate possible disaster through yielding of these weak spots in a forceful contraction. To the isometric phase of the ventricle is assigned the all important rôle of producing the arterial pulse by a kind of impact wave transmitted through the semilunar cusps and over the entire blood column of the arterial tree. This view of the etiology of the pulse can hardly fail to impress most students of cardiac physiology as quite unorthodox but it serves effectively in introducing a discussion of blood pressure in which a more startling view is set forth, namely, that diastolic pressure as usually determined is a misnomer. At this juncture an old and somewhat overlooked part in cardiac anatomy is brought into a major rôle. The bulbus aortae, we are told, forms a kind of elastic compensating chamber that exerts a continuous (systolic) pressure for the blood movement.

The final chapter of the book relates mainly to the mechanism of lymph flow. A discussion is given of the physicochemical and other factors, but the emphasis is given to the part played by the pulse as a propulsive force that drives the lymph.

The format of the book is good, the style is generally clear and agreeable, and the mistakes are few, but the substance of the arguments fails to carry conviction. Modern methods of recording, with sensitive instruments, simultaneously

the changes in intraventricular pressure and the pulsations in a central and peripheral artery present stronger evidence concerning the etiology of the pulse than is obtained from arguments about the physical attributes of the events in a cardiac cycle. Similarly, experimental results on the intraarterial pressure and blood velocity leave no room for doubt as to the fact of a diastolic pressure in the sense that the term is usually applied.

*D. J. E.*

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## Original Communications

### PHLEGMASIA ALBA DOLENS AND THE RELATION OF THE LYMPHATICS TO THROMBOPHLEBITIS\*

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THROMBOPHLEBITIS may be defined as an association of thrombosis with an inflammatory change in a vein's wall. As to which is usually the primary process, that is, whether the thrombosis or the inflammation is at the bottom of the trouble, has never been settled. Although some states of the blood undoubtedly predispose to thrombosis—a matter as to which Bancroft<sup>1</sup> has recently made a very full report—some local factor in or about the vessel's wall would seem to be the immediate exciting cause. Every one has necessarily been rather vague in speaking of this factor, which is more often, perhaps, infectious than traumatic or degenerative. What used to be called marantic thrombi, for instance, thrombi which form in the veins of patients depressed by systemic disease, have been shown so many times to be associated with the presence of bacteria in the vessel's wall as to bring the element of infection very much to the fore. And, of course, the familiar milk-leg is even more often suspected of being secondary to uterine sepsis. But it is far from true that all sorts of thrombophlebitis have a bacterial origin. Indeed, among the several forms of the disease presently to be described are more than one with which infection appears to have little to do.

In all, there may perhaps be five principal varieties of thrombophlebitis:

- (1) Thrombophlebitis in varicose veins;
- (2) Phlebitis migrans;
- (3) Thrombosis due to injury;
- (4) Thrombophlebitis in previously normal superficial veins;
- (5) Phlegmasia alba dolens, for which the synonyms are milk-leg and deep (iliac or femoral) thrombophlebitis.

Of all these varieties the last is decidedly the most interesting as well as the most serious and disabling. The others will therefore be discussed first.

\*From the Surgical Service of the Peter Bent Brigham Hospital, Boston.  
Read before the New York Academy of Medicine, October 23, 1931.

## THROMBOPHLEBITIS IN VARICOSE VEINS

Very commonly indeed, thrombosis occurs in the varicose saphenous vein or some of its branches. The process is liable to begin in a very superficial tortuous vessel of the calf or lower thigh and to advance upward. Exceptionally, thrombosis does not reach the groin, but since it is always likely to progress until it meets a vigorous current, it will usually be found, if given time, to have involved the saphenous vein up to its entrance into the femoral, which, however, it never seems to enter. From a thrombosed varicose vein embolism is rare.

The cause of thrombosis in varix is undoubtedly the unhealthy state of the vessel's wall. As this becomes scarred and stretched, the endothelial lining may readily be cracked or even destroyed at some one spot, permitting blood to clot, and from this point thrombosis spreads. In a process of this sort infection is quite as likely to be secondary as primary except, perhaps, in the presence of a septic ulcer. On the whole, the evidence is that it is usually mild and unimportant. Sometimes, of course, the skin becomes red and hot over the thrombosed vessel, and the clot softens, breaking down in the end and calling for drainage. Most often the skin becomes somewhat adherent, showing a little pinkish color which soon fades to a pale brown. A moderate induration surrounds the vessel, which can be felt as a solid, tortuous cord.

In contrast with some other forms of thrombophlebitis, this sort never causes edema of the leg, and though it is anticipating the subsequent story to offer an explanation, it would seem that the superficial lymphatics, which accompany the principal venous channels, are not disturbed by inflammatory processes within varicose veins. It must be that in the course of the dilatation and sclerosis which the varicose vein undergoes, the lymphatics about it are gradually destroyed, their function being taken over by other channels. Otherwise considerable swelling of the lower leg would be inevitable.

As every one knows, the course of phlebitis in varicose veins is prolonged, tedious, subject to recurrence, and requires, or seems to require, rest in bed. Nor are the veins permanently obliterated for the future. Being readily canalized, they soon resume their former appearance and character. It is therefore advisable, on meeting this sort of phlebitis in its early, acute state, to put the patient to bed, to use heat to relieve discomfort and to quiet the local inflammation, and when in the course of perhaps a week, the vein can be felt as a firm cord, to remove it by a formal operation. There is every reason not to use the traditional ice-bag. It devitalizes the tissues, interferes with nature's process of repair, probably causes thrombosis to spread and gives less comfort than does heat.

To obviate embolism, the operation should begin at the saphenous opening, and if the skin at any point is adherent to the thrombosed vessel, it should be excised with the vein, making a clean wound. Such op-

erations greatly shorten the patient's disability and cure the varicosity besides. They can be performed, if necessary, under local anesthesia.

There are, however, satisfactory and less radical means of treatment. Fischer<sup>4</sup> has recommended making local pressure at what seems to be the upper limit of the thrombosis by infolding the skin with adhesive plaster, just as is done for umbilical hernia in an infant, enclosing the leg below this level in adhesive strapping and letting the patient go about as usual. Jaeger<sup>9</sup> substitutes an "elastoplast" bandage for the enclosing adhesive plaster. He reports favorable results in more than 100 cases, finding that embolism does not occur. Another variation upon this scheme has been suggested by O'Neil.<sup>14</sup> He injects a sclerosing chemical into the vein above the thrombosed part—all these methods seem to depend on identifying this level, a matter not always easy—in order to destroy locally the varicose vessel and limit extension of the thrombosis; then he applies a "Klebro" bandage as under the German system. He too reports excellent immediate results.

#### PHLEBITIS MIGRANS

This curious disease is most often seen as a complication of thromboangiitis obliterans. Upon any part of the limbs there may appear a tender, sore thickening in the course of a vein. There may even be a rough symmetry between two opposing extremities. The vein seems to be occluded, although in the one specimen I have excised no thrombus was found. For several days or even weeks the process remains stationary or progresses a little, without much regard to treatment. Then it is likely to jump to a new spot higher up and to disappear below. Those who have suffered from many attacks are inclined to pay no more attention to the disease than they are obliged to. Short of massage, which has been known to excite embolism, such use of the part as the inevitable soreness allows, seems justifiable. No local treatment is of much help, though rest and warmth are grateful. Even in individuals whose Buerger's disease seems to have become, in most respects, stationary, phlebitis migrans may recur indefinitely.

But not all thrombophlebitis of this sort is related to thromboangiitis obliterans. Equally curious local migrating and recurring forms appear, usually in males, coming on in early adult life and returning at irregular intervals thereafter. These persons have blood, or veins, of such a character that thrombosis readily occurs, particularly in the superficial vessels of the legs. As a rule, only a short length of vein is involved and there is little reaction about it. Trauma often excites the inflammatory process and therapeutic intravenous injections of almost any sort are liable to induce it. In the few patients of this kind whom I have seen, pulmonary infarctions have been rather common. No effective treatment is known, though vaccines made from bacteria of the patient's tonsils or root abscesses have been used with reported success.

## THROMBOSIS DUE TO INJURY

Odd sorts of injury rarely lead to thrombosis of even the deep veins. My own experience has been entirely with thrombosis within the muscular aponeurosis of the lower leg: on two occasions, after fracture of a metatarsal bone, and on another, after vigorous massage. A fatal embolism resulted in one instance and the postmortem examination showed that most of the numerous veins among the muscles were thrombosed.

If the patient undertakes to go about in such a state, that part of the leg below the knee becomes somewhat cyanotic, full and slightly edematous. Discomfort is usually marked. On going to bed, these signs almost completely disappear, leaving only the slightest cyanosis and some degree of deep tenderness. This appearance of quiescence is deceptive, however, for if the patient tries again to get about, the original signs reappear. Recovery may be slow; so slow, indeed, and so subject to recurrence that, after one patient had died of embolism, the femoral vein of another was ligated in Hunter's canal. Recovery seemed to be hastened by this step, but its principal advantage is that it offers insurance against pulmonary infarction or embolism.

These three sorts of thrombosis, or thrombophlebitis, much as they differ from each other, differ still more from the varieties now to be described, in which edema is a feature and involvement of the lymphatics appears to be a fundamental part of the disease.

## THROMBOPHLEBITIS IN HITHERTO NORMAL SUPERFICIAL VEINS

Thrombophlebitis in hitherto normal superficial veins is placed in a category by itself, partly because, though rare, it is a serious disease and partly because its description will aid in making clear the distinction between superficial phlebitis and phlegmasia alba dolens, a matter, as to which, in the past, there has been a great deal of confusion.

The serious quality of an extensive superficial phlebitis in veins hitherto quite normal lies in the lymph-stasis and ulceration which usually follow the acute attack. As will appear later, the veins and large lymph-trunks are closely associated, so that anything affecting the one necessarily involves the other. And whether or not thrombosis occurs in the superficial veins because of a lymphangitis about them or whether the lymphatics are secondarily involved in a violent inflammatory reaction of the vein's wall, the fact remains that local and general lymph-stasis of the superficial tissues drained by the great saphenous vein is likely to follow an active thrombophlebitis in that vein. During the attack, the skin over the course of the main vein and its principal branches is liable to be red, hot and indurated. After the attack has subsided, as the patient begins to get about, edema, induration and pigmentation in the particular areas drained by the lymphatics associated with the saphenous

system set in, and ulceration sooner or later follows. Ulcers and residual induration should be treated after the methods which have been found so useful<sup>6, 7, 8</sup> in the management of postphlebotic induration and ulceration in general and to which presently reference will be briefly made.

The background of a superficial thrombophlebitis is, as a rule, a debilitating disease, injury or operation, whether or not associated with sepsis, but it is uncommon enough to have been very little studied. Probably the superficial and the deep disease have often been confused. Actually they should never be, for, in a superficial thrombophlebitis, the reaction about the superficial veins, that is, the great saphenous system,



Fig. 1.—Generalized thrombophlebitis of the superficial (nonvaricose) veins—the late result. Pigmentation and scar formation mark the course of the lymphatics accompanying the superficial veins. This is especially evident in the left leg.

is perfectly evident, as well to the eye as to the touch. The veins, in at least some part of their course, are palpable as hard, tender cords; and some visible redness or pigmentation of the skin is always present. What cause confusion are the tenderness and pain so often evident during a deep phlebitis over the femoral vessels in Hunter's canal. Unfortunately the femoral canal is directly beneath the usual course of the great saphenous vein, so that when the physician palpates the inner face of the thigh, finding acute tenderness extending from the groin nearly down to the knee, he believes the process to be superficial, whereas, unless the saphenous vein is actually palpable, it is invariably deep.



## PHLEGMASIA ALBA DOLENS\*

The nature of this ancient disease, with its sonorous title, has long excited the interest of the medical profession but seems latterly to have been given up as a bad job. Under the guise of milk-leg, its cause once seemed plain enough. Cruveilhier<sup>3</sup> described it as an iliac thrombosis, an accidental extension from a beneficent postpartum clotting in the great uterine venous sinuses. And when Pasteur<sup>15</sup> had laid uterine sepsis to the streptococcus, and Widal<sup>17</sup> and others had discovered these bacteria in the walls of thrombosed uterine veins, the bacterial origin of a thrombophlebitis of the great pelvic veins could quite reasonably be explained. For it seemed plain that thrombophlebitis of the uterine veins must then have progressed into the common iliac, obstructing the venous return from the leg. But phlegmasia alba dolens is by no means confined to the puerperium, nor is it even confined to females. It is liable to occur in individuals of young adult life and middle age, who are for any reason long confined to bed, particularly by debilitating diseases, whether or not infectious, by operations and by injuries. And in these persons it differs in no way from its puerperal form.

It has a rather characteristic course which varies in severity from case to case. As a rule, although the clinical signs are often missed, the disease begins with an elevation of pulse and temperature which may last twenty-four or forty-eight hours. Then pain sets in, usually referred to the thigh, the groin, the knee, the calf, sometimes the perineum. This may creep on, associated with a dead, heavy feeling in the leg or it may be so severe as to resemble a sudden arterial ischemia, leaving the leg totally powerless. In twenty-four to forty-eight hours more, swelling begins, and in another day or so, the whole picture of phlegmasia alba dolens is established.

Swelling affects the entire leg, thigh, calf and foot. In its severest form, tension is so great that there is no pitting on pressure. The leg can hardly be moved, not only on account of the discomfort but because of its great size. With disease of a milder sort, tension is much less, and after a few days of mild pain, discomfort on attempted motion and moderate swelling, improvement sets in. By the end of two weeks, this mild disease, except for a little residual swelling on getting about, is over. But with the severer forms the outcome is quite different. For weeks, even months, the huge white limb remains unchanged, subsiding only to leave behind so much edema that the leg, though useful enough, must be spared and nursed thereafter.

What first attracted my attention to phlegmasia alba dolens were its late complications, that is, the states of local edema, induration and ulceration which occur six months, a year, two years, even ten years later.

\*In the following discussion, the painful white inflammation of a limb is described as if it occurred only in the leg. A somewhat similar but far milder disease I have twice noticed in the arm. It has hardly been described or studied, except in the serious permanent form which it assumes as a sequel to operations for cancer of the breast.

With these, no venous stasis or obstruction is associated; rather do they have the appearance of local lymph-stasis. Such a lesion is liable to appear first as a porky area upon the inner face of the calf over which the skin repeatedly desquamates. This area enlarges and other patches may form. Soon pigmentation occurs and finally ulceration which may be very extensive, painful and intractable. This progressive change apparently is due to local nonsuppurative infection superposed upon a chronic generalized lymph-stasis, which may have been very obvious or

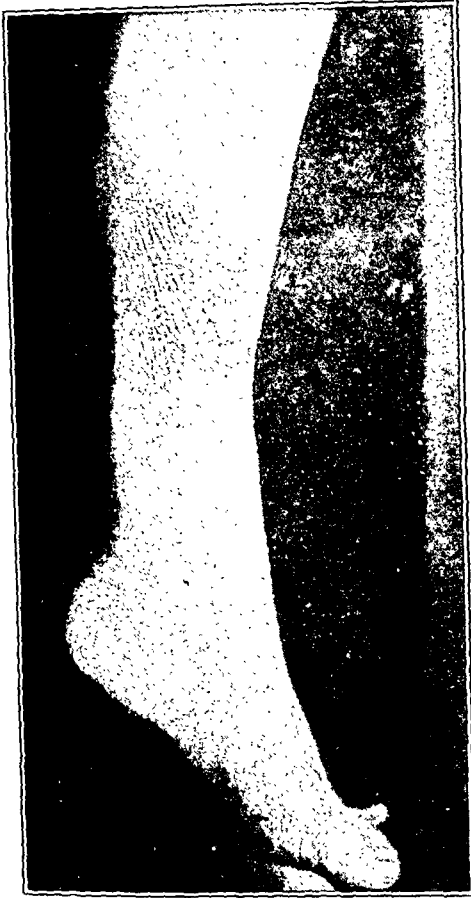


Fig. 2



Fig. 3

Fig. 2.—Postphlebitic edema after phlegmasia alba dolens in a typical situation—at an early stage. At the moment, the edema is receding, and desquamation of the skin is going on.

Fig. 3.—Postphlebitic edema and induration after phlegmasia alba dolens—a very advanced stage of ulceration. Such ulcers are best treated by a wide excision including the deep fascia, followed by a skin graft.

hardly noticeable. It seems to correspond, in a local form, to elephantiasis, which, it is generally agreed, results from repeated attacks of cutaneous infection in a limb already engorged with lymph. Obstinate ulcerations call for wide excision down to the unchanged tissues just beneath the deep fascia and for skin grafting or plastic operations. Local states of superficial edema and induration without ulceration can be treated with success, provided the deep lymphatics are open, by Kondoleon's<sup>10</sup> excision of deep fascial strips. Such treatment has been described in earlier publications.

Matas<sup>13</sup> was the first to recognize that lymph-stasis might follow upon thrombophlebitis, taking forms of actual elephantiasis hitherto unrecognized because there was nothing tropical in their origin. Then Halsted<sup>5</sup> and his associate, Reichert,<sup>16</sup> in studying the edemas of the arm following operations for cancer of the breast, ingeniously brought out the fact that occlusion of veins has little or nothing to do with edema of a limb and that occlusion of the lymphatics has everything to do with it. For if a dog's leg were entirely divided at the level of the upper thigh, leaving only the bone and the bare femoral artery and vein, and promptly reunited with the meticulous care which Halsted held before the world as the ideal surgical technic, an edema like that of milk-leg would set in. This edema would disappear within ten days, owing to the connections which the lymph vessels were able promptly to establish across the scar, but the really astonishing finding was this: that if, at the moment when the swelling had nearly gone, the veins were divided, the edema, after a slight delay, continued to subside as usual. In other words, swelling came on while the veins were patent and disappeared while they were occluded.

With such evidence in hand, the nature of phlegmasia alba dolens takes on a new meaning. One need not deny that venous obstruction is present. It may be serious enough to cause an extensive and unsightly collateral circulation to appear upon the thigh, groin and abdominal wall. But usually, and as compared with the edema, it is insignificant. The *white* swelling of a deep thrombophlebitis is, in fact clearly of a lymphatic nature. Obviously the great lymph vessels draining the leg are obstructed. Now it is known that no lymphatics empty into veins in the extremities or indeed elsewhere than where the thoracic duct enters the junction of the left jugular vein with the subclavian. Therefore clotting in a vein of a limb cannot directly obstruct any lymphatics. The question then arises: Can venous obstruction of itself cause edema? Halsted's experiment suggests that it does not. Moreover, one may repeatedly make multiple ligations of an animal's common iliac, external iliac and femoral veins without causing any edema whatever, and on the only occasion upon which I have ligated the common femoral vein, in a human being, the leg became for the time very dark, but neither then nor later, did any edema appear.

It is true, on the other hand, that if a sufficiently severe inflammatory reaction is set up in the main vein of a limb, edema will certainly follow. This has been proved experimentally in animals (Leriche and Jung<sup>12</sup>; Reichert<sup>16</sup>; Homans and Zollinger<sup>8</sup>), so that up to the point to which the story has been carried, it might be held: (1) that the edema of phlegmasia alba dolens is due to involvement of the lymphatics in a violent inflammatory reaction originating in the thrombosed vein; or (2) that inflammation of the lymphatics is sufficient of itself to account for the great white leg and that thrombosis within the vein is altogether sec-

ondary to the reaction outside it. Such statements imply that there is a close association of the blood vessels and lymphatics, a matter which should now be discussed.

Embryologically, the lymph vessels draining the limbs bud from veins, and the main lymph-trunks are intimately related to both veins and arteries. To put the matter briefly, there is a superficial cutaneous network and there are delicate longitudinal vessels in the deep skin, a combination which the various forms of superficial lymphangitis have made familiar to every one; there is a deeper network lying upon the muscular aponeurosis which is perhaps responsible for the postphlebitic indurations to which allusion has already been made; there are larger lymph vessels, which accompany the superficial veins, running with the lesser saphenous vein into the popliteal space and with the great saphenous vein into the group of lymph nodes at the saphenous opening; and, finally, there are large, trunk-line lymphatics which pass up with the femoral vessels to the groin. Here all the lymphatics of the leg, both superficial and deep, must join, and having joined, they pass along the external and common iliac vessels through the iliac glands and on into the receptaculum chyli. Therefore, to bring about lymph-stasis of the entire leg, it is only necessary to block the larger lymphatics at some point between the saphenous opening and the aorta. This, of course, makes the relation between the great lymphatics and blood vessels of the pelvic brim particularly interesting.

To William Cruickshank<sup>2</sup>—William Hunter's pupil—we owe most of our knowledge of these relations. He followed the absorbents, as he called them, by injections of air and of mercury, and gives the following succinct description: "The large absorbents of the lower extremity are formed into two sets, superficial and deep-seated; the superficial set accompany chiefly the cutaneous veins, and the deep-seated accompany the arteries." As for the deep lymphatics, he says: "From the glands in the ham, two grand trunks . . . run on either side of the femoral artery. These frequently communicate with one another by cross canals and their branches sometimes form circles which completely surround the artery." At the groin, the vessels he describes enter lymph nodes, emerging as two, four or even six trunks. From these there develops what he calls the "plexus iliacus externus."

Now if every one were not obsessed by the thought that phlegmasia alba dolens is a disease of the veins, the question might be raised whether it is not primarily a disease of the lymphatics. Suppose for a moment that there were such a thing as a deep lymphangitis—and no one seems to know whether there is or not—a violent inflammatory reaction would then take place actually within the arteriovenous sheath, affecting both the great vein and the artery of the limb. The vein, because of the active inflammation about it, would almost certainly become thrombosed, and the artery, if not thrombosed, might be thrown into a state of spasm.

At the same time, if the process took place at or above the saphenous opening, the whole leg would become swollen with lymph. Within the sheath, and depending upon the violence of the process, there would be an exudate, gluing together artery, vein and lymphatics. If this were

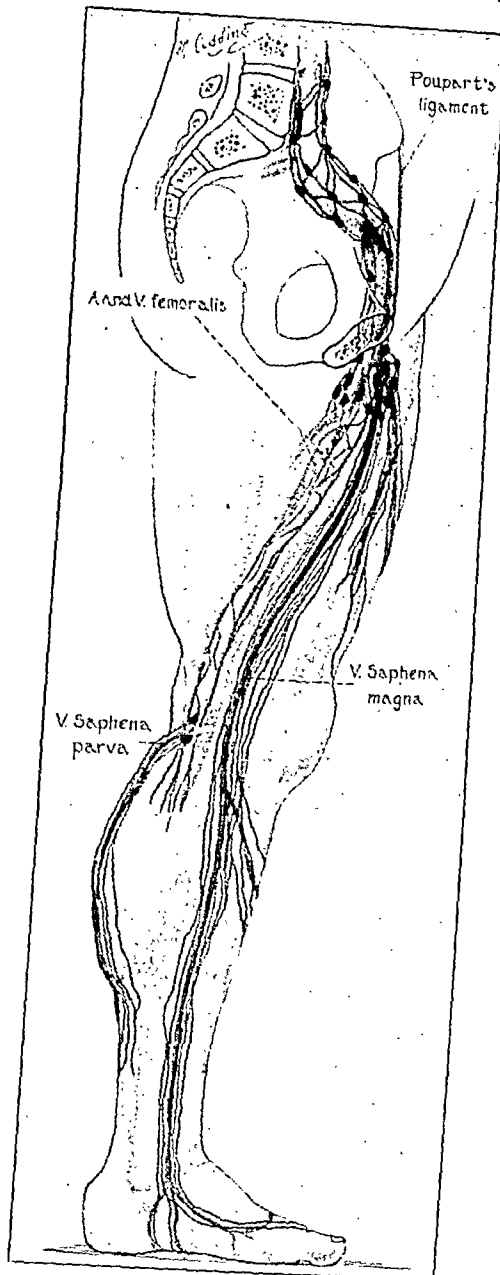


Fig. 4.—A semi-diagrammatic representation of the principal lymph vessels of the leg. The femoral artery and vein are indicated by a tone fainter than that of the superficial veins. The large femoral lymph vessels are shown as Cruickshank describes them, that is, closely surrounding the artery rather than the vein.

resolved, leaving little scar, no permanent disability would remain. If it became a densely organized scar, permanent lymph-stasis would follow.

Cruickshank<sup>2</sup> speaks of the lymphatics as being related to the great arteries rather than to the corresponding veins. Some years ago, a woman, about fifty years of age, presented herself at the Brigham

Hospital. Many years before she had suffered, in the course of a pelvic peritonitis, from phlegmasia alba dolens. The leg, however, had never been greatly swollen. The really striking change was toward ischemia. No actual pulsations could be felt at or below the left groin, and there was present, just above the ankle, an area of gangrene. In the course of a lumbar sympathetic neurectomy, which was of great benefit to her, it was possible to examine exactly the brim of the pelvis, where no sign of a vein could be made out and no suggestion of an arterial pulsation. Apparently both vein and artery had been destroyed by the earlier inflammatory process.

Obviously the most advantageous way to carry the matter further, was to examine, on the operating table, the state of the great artery and vein at the pelvic brim in a well-marked instance of phlegmasia alba dolens. Such an operation would be justified if it should prove that opening the arteriovenous sheath actually released local tension—a sort of *decompression*—and restored, in some degree, the flow of lymph.

By good fortune a young negro presented himself for treatment suffering from as high a grade of phlegmasia alba dolens as is often encountered. The disease complicated pneumonia, coming on with fever and with severe pain in the left leg, and leaving him, at the end of eight days, with a leg so tense that it neither pitted on pressure nor changed in any degree from day to day. The temperature remained steadily elevated between 100° and 101° F.

At the operation, the abdomen was opened a little to the left of the midline, exposing the left pelvic brim. As far as the left iliac vessels were concerned, all landmarks were obliterated. It was barely possible to feel the arterial pulsation, and whether or not a solid clot filled the vein was at first impossible to say. However, what seemed to be the sheath was finally split, revealing porky, lymph-soaked, vascular tissue so adherent to the great vessels that the vein was only discovered by accidentally cutting into it and the artery identified by its pulsation. The deeper coats of the vein seemed relatively normal, and a dark clean clot filled it solidly. In view of the vivid quality of the reaction about both artery and vein and the reactionless appearance of the clot, it seemed that the infection, if infection there were, must have begun outside the vein rather than within it; certainly the clot was the least striking part of the process. Opening the arteriovenous sheath proved quite difficult, owing to the very vascular exudate within and about it. The common iliac artery and vein could not have been exposed without unduly prolonging the operation, and so the sheath of only the external iliac vessels was split down to a point a little below the inguinal ligament. The operation was completed by loosely closing the peritoneum.

The result was dramatic. On the day following, the patient felt the tension lessen decidedly, and within three days the swelling had gone down remarkably. At a second stage, the femoral sheath was opened in

Scarpa's triangle and Hunter's canal. It is doubtful whether this part of the operation was necessary. Certainly it would have been better to have substituted decompression of the common iliac sheath. But, at least, exploration of the thigh showed that the most active seat of the disease was *above* the inguinal ligament and that it died out in intensity as it descended toward the knee. As a first attempt, this operation can perhaps be considered a success. Some two weeks after the first stage, the swelling, which bade fair to last for many weeks or months, had disappeared, yet in some degree it has since returned, that is, since the patient has gone about again, perhaps because of the incompleteness of the iliac decompression.

One other patient, suffering from a more chronic though less severe disease, has been treated in a similar way, and from this second experience it must be concluded that if the operation is to be of any value, it must be done early; for on this occasion the whole sheath has been converted into a nearly solid scar. The artery was shrunken, in a state of spasm, the vein the less involved of the two vessels. It almost seemed as if the dissection left more damage behind than it relieved. Whether a safe and useful procedure can be devised for opening the sheath from the highest point involved down to the saphenous opening—obviously the most important area—is not yet clear. But at least operation can be said to have revealed the quality of the local process, that is, a *nonsuppurative inflammation marked by a vascular exudate within the iliac and, to a lesser degree, the femoral arteriovenous sheath, affecting artery and vein alike.*

A little more light is shed upon the nature of phlegmasia alba dolens by two other recent observations. If it is a disease of lymphatics, capable of affecting the artery within the common sheath quite as much as the vein, some evidence of arterial disorders, over and above those already described, ought to be forthcoming. During the past winter, a man, forty-three years of age, entered the medical service of the Brigham Hospital suffering from pneumonia. He was not particularly ill, but for some reason was given a hypodermoclysis in the outer part of the right thigh. There remained locally, after what had seemed a normal absorption of the saline solution, a small tender lump, and ten days after the infusion, a slight, tender swelling of the femoral and lower iliac lymph nodes appeared. At the same time, the patient suffered a moderately severe pain in the right thigh, which, within twenty-four hours, was followed by moderate edema of the entire leg. Naturally, it was decidedly interesting to see an instance of phlegmasia alba dolens quite clearly of lymphatic origin,\* but it was even more fascinating to

\*A somewhat similar case was reported, in 1807, to the Massachusetts Medical Society, by Edward Wyer.<sup>13</sup> At the onset of phlegmasia alba dolens, ten days after childbirth, acute swelling and pain in the lymph nodes at the groin and a streak the color of raspberry juice passing up the front of the leg were noticed. Wyer held the disease to "depend upon an accumulation of lymph in the limb . . . dependent on causes peculiarly connected with the puerperal state."

discover that the femoral pulse on this side was nearly obliterated and that no pulsations could be felt below the groin. In attempting to take the blood pressure at the popliteal space, one or two arterial beats were heard to come through the cuff at the same pressure as was present in the opposite leg; which makes it clear that the vessel on the affected side was still patent though much narrowed. If this observation is acceptable, it may be believed that the initial pain of milk-leg, which often is so severe as to suggest arterial occlusion, is, in fact, due to an ischemia of arterial origin. Certainly the artery is contracted when seen in explorations of the acute disease. And unless an earlier observation is erroneous, it may even be obliterated. Is it too wild a suggestion to hint that the instances of gangrene which have been reported in the past as complications of typhoid fever and of pneumonia may really have been due to violent arterial spasm or even thrombosis, that is, arterial exhibitions of a state which, in its common form, would be *phlegmasia alba dolens*? Doubtless the arterial side of the disease can readily be observed if only one looks for it.

There is yet one more matter bearing on the nature of *phlegmasia*. If the characteristic edema is not due primarily to thrombosis within the iliac vein but to a reaction within the arteriovenous sheath, it should be shown that infiltration of this sheath without thrombosis is capable of causing a typical edema. As to this there is actually some clinical evidence. A patient who was operated upon at the Brigham Hospital for biliary obstruction and who died of hemorrhage, happened to have bled into the retroperitoneal tissues of the left pelvic brim. Blood infiltrated the arteriovenous sheath, causing a well-marked edema of the entire corresponding leg, yet without any thrombosis within the vein.

But even more authoritative observations as to the effect of perivenous inflammation in causing swelling of a leg have been recorded by Leriche,<sup>11</sup> and by Leriche and Jung.<sup>12</sup> They made injections of salicylate of soda (30 to 40 per cent solutions) not only into the lumen of the iliac and femoral veins but also into the adventitial sheath about them. In either case, a severe perivenous reaction followed and extensive edema usually occurred. They conclude that occlusion of the veins has little or nothing to do with the result, that perivenous inflammation has everything to do with it and that involvement of vasomotor nerves causes the edema. It seems more reasonable to suppose that involvement of the lymphatics rather than vasomotor fibers is responsible, but doubtless Leriche would say that I had assumed the rôle of the devil and was quoting scripture for my own purposes.

Such, in brief, is the information which bears upon the nature of *phlegmasia alba dolens*. Are its exhibitions due fundamentally to thrombosis and an inflammatory reaction within the principal vein draining the limb, that is, a primary thrombophlebitis? All of its aspects cannot be explained in this way, and the evidence supporting this



hypothesis is chiefly traditional. Is it due, on the other hand, to a deep lymphangitis, which secondarily affects the blood vessels occupying the same sheath? The evidence strongly favors this hypothesis, even though the source of infection is not usually evident. And here this aspect of the matter must be left for further study. One might suppose that a primary deep lymphangitis within the pelvis could arise in various ways: from the uterus, from the rectum and sigmoid flexure, from the prostate, seminal vesicles and bladder, and of course from the leg itself, as in the instance cited. In any case, all infections taken up by the lymphatics of the pelvis or the legs have direct access to and *must indeed necessarily pass through the great lymph vessels about the external and common iliac blood vessels*. Here, certainly, is the seat of the lesion obstructing the lymphatics draining the leg.

But it must not be taken for granted that the venous side of the disease can be neglected. Venous thrombosis must inevitably be a part of it. The great white swollen leg shows at least a slight cyanosis, and, as the edema recedes, this becomes increasingly evident. If the thrombosis extends down to the popliteal space, there are usually visible dilated anastomotic vessels about the knee joint. And, unless the principal vein is soon recanalized, the anastomotic veins, particularly those connecting the saphenous system with the superficial veins of the abdominal wall, become permanently enlarged, perhaps varicose. In some few cases, both legs are involved, though unequally, as shown in Fig. 3, but whether or not a bilateral process implies that the lower part of the vena cava is affected seems not to be known.

Embolism is, on the whole, unusual. It appears less likely to occur in the course of an outspoken plegmasia alba dolens than from obscure sources of thrombosis near an operative field. That is, perhaps, consistent with the idea of a perivenous inflammation causing a secondary clot in the iliac vein, for such a clot, except perhaps in the presence of suppurative sorts of infection, would be likely to have a uniform character, unlikely to undergo a septic softening, and would be solidly adherent to the vein's wall. In most instances, then, fear of embolism need hardly militate against any proposed treatment.

The treatment of phlegmasia alba dolens ought to be planned to get rid of the edema at the earliest moment, to restore the lymphatic circulation and to forestall the late complications. There is no reason, at an early stage, for doing anything but giving such opiates as are needed and elevating the leg. There is every reason for not using ice on the leg, for the basic lesion is not there, and even if it were, ice would be the worst possible remedy for it.

As soon as fever has disappeared and tension has lessened a little, the leg should be exercised in bed, first by setting and relaxing the muscles and then by actually moving it. There is no objection, even, to light massage. Such measures are no more liable to cause embolism than taking a

bed-bath or using a bed-pan. As the swelling goes down, the patient should begin to exercise the leg in a dependent position—the main thing being *never* to let it remain dependent except when exercising it. For the more readily lymph is drained from the limb and the fewer hours out of each twenty-four the tissues are kept soaked in lymph, the less liable are secondary infections to occur. The late complications and their treatment have already been described. It is clear that only when lymphstasis is superficial and local, can efforts to drain lymph from the superficial tissues into the deeper parts by the Kondoleon procedure have any success. To attempt such an operation in the face of generalized lymphstasis in the leg, due to plugging of the principal lymph vessels above the groin, is utterly unreasonable.

Operative treatment of phlegmasia alba dolens is in the experimental stage. It should only be used upon the worst cases and should probably be confined to splitting the sheath over the iliac vessels. There is no doubt that, if performed promptly, it causes the swelling to recede in a remarkable way, but whether an abdominal operation should be added to the patient's difficulties is not yet clear. Evidently, since the obstruction is primary about the great iliac vessels, there and not elsewhere is the place to attack. Yet the operation requires some degree of skill, and since it entails, in the treatment of a disease not in itself fatal, a possible risk to life, it must be shown to have decided advantages before it can be accepted even as a basis for further progress.

To recapitulate, there are forms of thrombophlebitis dependent upon an unhealthy state of the vein's wall—the varicose type—and peculiar sorts, partly of local origin and partly due, perhaps, to an abnormality of the blood—phlebitis migrans. There are also venous thromboses of traumatic origin. But thrombophlebitis which affects the previously healthy veins draining the lower limbs, particularly the familiar scourge, phlegmasia alba dolens, appears to be secondary to a nonsuppurative lymphangitis, which from its situation, is able to attack artery as well as vein. And the principal exhibitions of such a disease are neither venous nor arterial, but lymphatic.

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# SOME CLINICAL FEATURES OF CORONARY ARTERY DISEASE\*†

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IT WAS Edward Jenner,<sup>1</sup> in the latter part of the eighteenth century, who first suggested the probable relationship between calcareous deposits in the coronary arteries and that "disorder of the breast" to which his contemporary, Heberden, gave the name "angina pectoris." With Jenner's observations, followed soon after by those of Parry, originated the concept that there was an association between disturbances in the coronary circulation and the manifestations of a disordered heart. In 1884, Leyden<sup>2</sup> gave an excellent description of coronary sclerosis and thrombosis, and for the first time satisfactorily correlated symptoms, signs and pathological changes. The evolution of sharply delineated clinical pictures has been slow, though stimulated during the past twenty years by renewed interest in acute coronary obstruction. In the development of our knowledge concerning this condition, the paper of the Russians, Obrastzow and Strashesko<sup>3</sup> in 1910, and the publications of J. B. Herrick<sup>4</sup> in 1912 and 1919, will stand, together with Leyden's account, as historic landmarks.

What are the various affections which may involve the coronary arteries? Data on this point have been obtained from the autopsy records of the Presbyterian Hospital covering the ten-year period 1920

TABLE I  
ETIOLOGIC TYPES OF CORONARY DISEASE WITH ASSOCIATED PATHOLOGIC STATES.\*  
THEIR RELATIVE FREQUENCY IN 148 AUTOPSIES AT THE PRESBYTERIAN HOSPITAL,  
NEW YORK (1920 TO 1929, INCLUSIVE)

|  |     |
|--|-----|
| 1. Arteriosclerosis                    |     |
| a. Atheroma                            | 110 |
| b. Calcification                       |     |
| c. Stenosis                            |     |
| d. Occlusion                           |     |
| e. Thrombosis                          | 22  |
| f. Infarct of myocardium               | 56  |
| g. Aneurysm of heart                   | 5   |
| h. Rupture of heart                    | 3   |
| 2. Syphilis                            |     |
| a. Stenosis or obliteration of orifice | 12  |
| b. Infarct of myocardium               | 3   |
| 3. Rheumatic fever                     |     |
| a. Arteritis                           | 2   |
| 4. Embolism                            | 1   |
| 5. Periarteritis nodosa                |     |
| a. Arteritis                           | 1   |

\*Obviously, in a number of instances, more than one lesion was present.

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to 1929, inclusive.\* During this time, 148 cases (10.7 per cent of all the autopsies) showed lesions in the coronary vessels. The etiological types of pathological condition observed, together with their relative frequency, are shown in Table I.

Syphilis of the coronary arteries is seen almost exclusively in association with specific aortitis, and assumes clinical importance when the orifice of one or both coronaries becomes stenosed or obliterated. In such cases, as pointed out by von Glahn,<sup>5</sup> the abnormally high origin of the vessels predisposes to their involvement by the syphilitic process in the aorta. Syphilitic arteritis of the smaller intermuscular branches, described by Warthin,<sup>6</sup> was not encountered in this series; nor was coronary involvement found in cases of thromboangiitis obliterans or erythremia. The coronary lesions of rheumatic fever, for the present, are of interest chiefly to the pathologist. Clearly, the arteriosclerotic group, with the concomitant morbid changes in the heart, is numerically by far the most important. The relatively high incidence of infarction of the myocardium unassociated with recent thrombosis, is noteworthy. Some of these infarcts no doubt are the result of an old, acute thrombotic occlusion. Many, however, appear to follow the more gradual closure of a branch, due to sclerotic changes.

The infrequency of embolism of a coronary artery also deserves mention. In a series of 3093 autopsies performed in the course of twenty-four years, this condition was met with but three times. It occurred once in a young man with vegetative endocarditis of the aortic valve, who died suddenly due to the plugging of the orifice of the left coronary by a piece of vegetation. A second instance was observed in a boy of nineteen years, who suffered from subacute mitral and aortic endocarditis due to *Bacillus influenzae*. The coronary embolus was small and death was gradual. The third case was that of an eighteen-year-old boy, who died suddenly after an enema. The myocardium showed a curious hydropic degeneration, with fibrosis and infarction. There were thrombi in the right ventricle, and an embolus was found in the anterior descending branch of the left coronary artery.

That heart disease is now the leading cause of death, and that its mortality curve has been rising steadily for the past twenty years is a matter of common knowledge. But that the increasing number of deaths from diseases of the heart occurs almost entirely in persons over the age of forty-five years, is not so generally appreciated.<sup>7</sup> In the younger age groups, the rate is actually falling. How is the increasing number of cardiac deaths in older individuals to be explained? It is due, in large measure, to the fact that more people are living to the "heart age," that is, they survive to that period of life when degen-

\*The period was begun with the year 1920, because by this time the various features of coronary artery disease were sufficiently well known to make valid a comparison between autopsy and clinical records. The period was terminated with the year 1929, because of re-arrangement of the hospital service after this date. Subsequent figures, therefore, were not comparable. I am indebted to Dr. James W. Jobling for permission to utilize the Records of the Department of Pathology.

erative processes affect the circulatory system to a sufficient degree to cause functional impairment. In addition, the growing body of knowledge concerning cardiovascular conditions has resulted in more accurate diagnosis. We are becoming increasingly familiar with the protean manifestations of circulatory disorders, and it is now rare to find the cause of death given as "acute indigestion" or "senility."

The question naturally presents itself as to whether affections of the coronary arteries are likewise showing a rising trend in their incidence. Again, the autopsy files of the Presbyterian Hospital were consulted, using the material recorded during the ten-year period 1920 to 1929, inclusive. The results of the analysis are shown in Table II. It is ap-

TABLE II  
PERCENTAGE OF CASES OF CORONARY ARTERY DISEASE\* IN RELATION TO  
TOTAL NUMBER OF AUTOPSIES, 1920 TO 1929, INCLUSIVE  
(PRESBYTERIAN HOSPITAL, NEW YORK)

| YEAR         | TOTAL NO. OF<br>AUTOPSIES | NO. OF CASES OF<br>CORONARY DISEASE | PERCENTAGE OF CASES<br>OF CORONARY DISEASE |
|--------------|---------------------------|-------------------------------------|--|
| 1920         | 124                       | 16                                  | 12.9                                       |
| 1921         | 91                        | 12                                  | 13.2                                       |
| 1922         | 147                       | 13                                  | 8.8  |
| 1923         | 123                       | 7                                   | 5.7  |
| 1924         | 127                       | 13                                  | 10.2                                       |
| 1925         | 118                       | 14                                  | 11.9                                       |
| 1926         | 144                       | 20                                  | 13.9                                       |
| 1927         | 115                       | 13                                  | 11.3                                       |
| 1928         | 151                       | 11                                  | 7.3  |
| 1929         | 240                       | 29                                  | 12.1                                       |
| Total period | 1380                      | 148                                 | 10.7                                       |

\*Anatomical diagnoses included are: arteriosclerosis of coronary artery, thrombosis of coronary artery, embolism of coronary artery, syphilitic stenosis or obliteration of orifice of coronary artery, infarct of heart and aneurysm of heart. Cases filed under more than one heading are counted only once.

parent that, although the percentage of cases of coronary disease in relation to the total number of autopsies has shown some variation from year to year, yet there has been no distinct trend either up or down. In both 1920 and 1929, the figure was 12 per cent. The evidence presented by this particular group of cases affords no support for the current impression that an increasing proportion of the population is dying of coronary artery disease. No other comparable set of figures has been published. Before drawing a general conclusion, it will be necessary to analyze a large and assorted material.

The clinical diagnoses during the same ten-year period were then tabulated for comparison with the autopsy findings (Table III). The analysis was based upon the percentage of cases diagnosticated as coronary artery disease, in relation to the total number of admissions to the medical service. The difference in trend is striking, for with minor fluctuations, the percentage rises from 1.1 in 1920 to 4.3 in 1929—a fourfold increase. Tabulation of the cases by age groups showed that

the increase in the latter part of the period was not due to the fact that during these years a greater number of elderly patients was admitted to the hospital.

How can this discrepancy between autopsy and clinical records be reconciled? I believe that the explanation can be stated briefly and in modern parlance. Thus, it may be said that during the last two decades we have grown to be "heart-minded"; in the past ten years we have become "coronary-conscious." Many of the milder, nonfatal and atypical forms of coronary disease are being recognized with increasing frequency. For this reason, the figures for the later years probably more nearly approximate the truth.

TABLE III

PERCENTAGE OF CASES DIAGNOSED AS CORONARY ARTERY DISEASE\* IN RELATION TO TOTAL NUMBER OF ADMISSIONS TO MEDICAL SERVICE, 1920 TO 1929, INCLUSIVE (PRESBYTERIAN HOSPITAL, NEW YORK)

| YEAR         | TOTAL NO. OF MEDICAL ADMISSIONS | NO. OF CASES OF CORONARY DISEASE | PERCENTAGE OF CASES OF CORONARY DISEASE |
|--------------|---------------------------------|----------------------------------|---|
| 1920         | 1886                            | 20                               | 1.1                                     |
| 1921         | 1837                            | 17                               | 0.9                                     |
| 1922         | 1820                            | 19                               | 1.0                                     |
| 1923         | 1587                            | 13                               | 0.8                                     |
| 1924         | 1677                            | 35                               | 2.1                                     |
| 1925         | 1720                            | 33                               | 1.9                                     |
| 1926         | 1639                            | 47                               | 2.9                                     |
| 1927         | 1651                            | 38                               | 2.3                                     |
| 1928         | 1581                            | 58                               | 3.7                                     |
| 1929         | 2198                            | 94                               | 4.3                                     |
| Total period | 17,596                          | 374                              | 2.1                                     |

\*Clinical diagnoses included are: arteriosclerosis of coronary artery, thrombosis of coronary artery and infarct of heart. Cases filed under angina pectoris are also included if the record suggests that coronary disease was the basic pathologic state. Cases filed under more than one heading are counted only once.

It has been pointed out that arteriosclerosis, with the various associated lesions in the myocardium, is the commonest form of coronary affection. We apply to it the name of disease because there is an ill-defined transition zone between those changes incident to the normal processes of senescence and the morbid states which are regarded as pathological. For clinical purposes, it may be said that disease exists when the degenerative process has induced alterations in a tissue or organ in such a manner or in such a location that symptoms and signs of functional impairment become manifest. Usually, coronary sclerosis is part of a generalized arterial degeneration; occasionally, only the coronary bed appears to be involved to a significant degree.

Concerning the causes which predispose to degenerative changes in the coronary vessels but little is known. Heredity undoubtedly plays a rôle, for several members of a family may suffer from the anginal syndrome and die in the agony of an attack. As Osler phrased it, "in the make-up of the machine, bad material was used for the tubing."

Men are more frequently affected than women. Evidences of impairment of function usually appear after the age of forty, and the fifth may well be called the dangerous decade. The part played in etiology by diet, by infections, general and focal, as well as by tobacco, alcohol and endocrine imbalance, is not clearly defined. In patients with diabetes mellitus, coronary disease is encountered with relative frequency.<sup>8</sup> Obesity, especially in the hypertensive, undoubtedly places an added burden on the circulation; and hypertension itself often precedes, or accompanies atheroma. Warthin's<sup>6</sup> contention that syphilis predisposes to coronary sclerosis and its resultant cardiac pathology, finds no support in the observations of others.<sup>9</sup> There is much current talk concerning the specific deleterious effects of the hurry, worry and speed of modern life upon the cardiovascular system. It is difficult to prove such a relationship, for many factors must be taken into account. And it is well to bear in mind that arteriosclerosis is a disease of antiquity, found in the mummied corpses of Egyptians who lived 3500 years ago. The cause of truth is not furthered by drawing hasty and ill-founded inferences based upon circumstantial evidence.

The pathological changes in the heart which result from sclerosis of the coronary arteries will, of course, vary according to the extent and location of the vascular lesions. Small isolated plaques may cause no damage to the myocardium. Impairment of the circulation of the heart muscle may result in patchy fibrosis. Stenosis and occlusion are often followed by the formation of an infarct, and if the area of softening and subsequent thinning of the wall is extensive, aneurysmal dilatation of the ventricle follows. If the changes are diffuse, the heart enlarges, chiefly by hypertrophy. It is axiomatic that an enlarged heart is a diseased heart, though not necessarily one which is functionally inadequate.

It has been pointed out by Gross<sup>10</sup> and by Oberhelman and Le Count<sup>11</sup> that there are wide variations in the distribution and anastomoses of the coronary arteries, in different individuals and at different periods of life. It is reasonable to expect, therefore, that the manifestations of disturbances in the coronary circulation will be variable, due in part to anatomical conditions, and in a measure to other individual constitutional factors. Clinically, the cases of coronary sclerosis (exclusive of thrombosis) may be divided, according to their presenting symptoms, into four groups: (1) those with cardiac insufficiency; (2) those with cardiac pain; (3) those with digestive disturbances; (4) those without symptoms, and sometimes without signs—the latent type. Obviously, there are many mixed cases with symptoms from more than one group.

(1) *The heart failure group.* A majority of the cases which were formerly called "chronic myocarditis," and to which the term "fibrosis of the myocardium" is now applied, are the result of sclerotic changes



in the coronary arteries. Frequently it is the smaller branches which are involved. The heart is usually enlarged. Hypertension is sometimes, though not necessarily, present. The patients are most often men in the fifth or sixth decades of life. Signs of valvular disease are usually absent, but an apical systolic murmur may be heard, sometimes due to a flabby and dilated mitral ring. Anatomical mitral insufficiency may result from extension of the sclerotic process from the aorta to the anterior cusp of the mitral valve; a similar atheromatous or calcified lesion may deform the aortic valve segments, with the production of leakage or narrowing at the aortic orifice.

The symptoms of cardiac insufficiency are insidious in their onset. Slight dyspnea after a degree of effort which was habitually untended by discomfort, is an early harbinger of trouble. Swelling of the ankles above the shoe tops, toward evening, follows ere long. Cough, a sense of fullness in the epigastrium, due to a swollen liver, and inability to recline comfortably in bed on the customary number of pillows, are later evidences of advancing heart failure. Tachycardia and irregularity of the heart's action, in the form of premature beats or auricular fibrillation, may cause the patient to complain of palpitation. I have been particularly impressed by the frequency with which premature beats of auricular origin are observed in these cases. Heart-block, partial or complete, is one of the forms of arrhythmia more rarely encountered. Changes in the form of the electrocardiogram, if present, afford confirmatory evidence of myocardial fibrosis, and their character may be of decided aid in estimating the severity of the cardiac damage. Often, however, the graphic record shows little or no deviation from the normal, in spite of the clinical picture of advanced failure.

Once the signs of myocardial insufficiency have appeared, the course is usually progressively downward. Each successive break in compensation is followed by slower and less complete recovery. Arteriosclerotic closure of a coronary branch, if gradual, may be unattended by symptomatic disturbance. If the obstruction of the lumen is sudden, discomfort is often marked. As in thrombotic occlusion, there may be pain, nausea, vomiting and occasionally transitory cardiac irregularity due most frequently to premature beats or auricular fibrillation. If the obstructed vessel is of fair size, there is formed an infarct of the myocardium. Subsequently, aneurysmal dilatation of the ventricle may develop. In the late stages of failure, paroxysms of nocturnal dyspnea (so-called cardiac asthma) are not uncommon and may be accompanied by pulmonary edema. Yet, with careful management, some of these patients are able to carry on at a lowered level of activity for a number of years. The end may come gradually, from increasingly severe heart failure, or quickly, from acute coronary obstruction or a cerebral hemorrhage. If the kidneys are affected, uremia is sometimes the terminal event.

(2) *The pain group.* The cases characterized by attacks of substernal or precordial pain are commonly called by the generic term "angina pectoris." On previous occasions, I have endeavored to point out the undesirability of applying to this symptom a designation which, historically at least, carries with it the implication of a particular disease.<sup>12</sup> Pain in the chest may be an expression of a number of basic pathological states. It is profitable and indeed, essential, to consider the diagnostic problem from its etiological, anatomical and functional aspects, if intelligent therapy is to be given and a reasonably accurate prognosis is to be attempted.

The mechanisms by which pain impulses originate in the heart and are transmitted from it to distant points of reference, are as yet but imperfectly understood. It would require too much time to give them adequate consideration here. It is sufficient to say that there is increasingly convincing evidence, both clinical and experimental, which indicates that heart pain, paroxysmal or prolonged, is usually of coronary origin and results from myocardial ischemia.<sup>13</sup> In a study of the pain in intermittent claudication, Lewis<sup>14</sup> has recently shown that chemical or physicochemical factors are also concerned in its production. As he has indicated, analogous conditions may prevail in pain of cardiac origin. Furthermore, transient changes in the form of the electrocardiogram during brief attacks strongly suggest the possibility that the anoxemia is in part functional and in such paroxysms may arise from spasm of the coronary arterioles.<sup>15</sup>

The characteristics of what may be called a typical attack are well known. The pain may occur not only after effort or emotion, but at rest, and not infrequently at night, in bed. It varies in intensity, in part according to the sensitivity of the individual to painful stimuli. A sense of substernal oppression may be as significant as the sharpest twinge. There are many equivalents of breast pang, such as headache, dizziness, a sudden feeling of great weakness, sweating (sometimes unilateral in distribution), nausea or vomiting.<sup>16</sup> An unusual opportunity to observe the substitution of paroxysms of dyspnea for pain was afforded recently. A man, aged forty-four years, with coronary sclerosis and attacks of pain so severe that he had been completely incapacitated for eight months, received paravertebral injections of alcohol into the first five dorsal rami two and one-half years ago. He was completely relieved of the paroxysms and was able to return to work. He came to the clinic three weeks ago, complaining of attacks, occurring both after effort and at rest, during which he became suddenly short of breath and actually gasped for air. The attacks were accompanied by an aching sensation in the left elbow. All discomfort was promptly relieved by nitroglycerine. Such pain equivalents are frequently confusing and I believe are often present in patients who die suddenly and who are said to have had no previous cardiac complaints.

(3) *The digestive group.* It is only in recent years that adequate emphasis has been placed upon the importance of digestive disturbances as part of the picture of myocardial disease. Both the gastrointestinal tract and the heart are innervated by large branches of the vagus nerve, so that reciprocal symptoms might well be anticipated. There are, in addition, numerous intercommunicating sympathetic pathways. Indigestion is one of the favorite disguises of coronary sclerosis; flatulence and belching are among its common manifestations. Many of these patients are treated for supposed ailments of the stomach, bowel or gall bladder. A paroxysm of cardiac pain may be referred entirely to the epigastrium; nausea and vomiting attract further attention to the abdomen as the source of trouble. The more violent digestive symptoms in acute coronary obstruction are of even greater interest and importance; reference will be made to them again under that caption.

(4) *The latent group.* It is hardly necessary to point out that the presence of coronary sclerosis is frequently overlooked during life and is found as a surprise at the post-mortem table. In a series of 86 consecutive, proved cases studied by Willius and Brown<sup>17</sup> at the Mayo Clinic, 34, or 40 per cent were of the latent type, in which there was insufficient subjective or objective evidence of cardiac disease to permit of its clinical identification. Coronary disease should be suspected whenever a chronic, nonvalvular affection of the heart is observed in an individual over forty years of age. Attention paid to the atypical manifestations will result in a higher percentage of correct diagnoses.

Thrombosis of a coronary artery may be considered as an episode in the natural history of coronary sclerosis, for the thrombus almost invariably forms in a vessel already the seat of atheroma or calcification. So, in a majority of instances, if a careful history is taken, or a complete examination is made prior to the attack, some evidence of previous cardiac disturbance will be discovered. The dramatic features of sudden obstruction of a large coronary branch impress themselves indelibly upon the memory of the observer. The agonizing and prolonged substernal or epigastric pain, the nausea, vomiting and belching of gas, the ashen countenance bathed in cold sweat, and the anxiety of the sufferer, all serve to define a picture which is now well known.<sup>18</sup> The blood pressure falls, the heart rate rises, and cardiac arrhythmias of various types may appear. The presence of a gallop rhythm indicates that the myocardium has been severely damaged.

Following the shutting off of the blood supply to an area of heart muscle, an infarct develops, varying in size with the caliber and number of occluded branches. If the infarct reaches the pericardial surface, a friction rub may be audible, often only for a short time. Necrosis of the myocardium is followed, after the lapse of some hours, by fever. The leucocyte count rises, at times soon after the occlusion, and may

be as high as 30,000. Almost invariably, even in the absence of leucocytosis, there is relative polynucleosis. Persistence of fever and leucocytosis for a number of days, or a rise in either or both, is strongly suggestive of progressive myocardial necrosis or intracardiac thrombosis.<sup>19</sup> Bits of thrombus within the ventricle may become detached, and depending upon whether the right or the left side of the heart is the site of infarction, emboli may be carried to the lungs or systemic circulation. Hemoptysis due to pulmonary infarction is relatively frequent; hemiplegia and the plugging of an artery in the leg are graver complications.

The electrocardiogram is often of great aid in differential diagnosis and is useful in following the progress of the cardiac lesion.<sup>20</sup> To consider it in detail is not within the scope of this paper. Three points should be kept in mind in the interpretation of the records: (1) form changes, if present, should not be regarded as etiologically specific; (2) successive changes from day to day, or week to week, afford evidence of altering conditions in the myocardium, and may indicate healing of the infarct or an advancing lesion; (3) a relatively normal record may be obtained, even though there is extensive damage to the heart muscle.

Much attention has been directed to the abdominal symptoms of coronary thrombosis, for they have led to great confusion in diagnosis. The acute cardiac upset has been mistaken for cholecystitis, cholelithiasis, acute pancreatitis, perforated gastric or duodenal ulcer, intestinal obstruction and hemorrhage into the suprarenal capsule. Surgical procedures have actually been attempted under these circumstances. So strongly have the abdominal manifestations of a coronary attack been impressed upon the minds of physicians, that there is now a tendency for the diagnostic pendulum to swing in the opposite direction. A case in point is as follows:

#### CASE REPORT

Mrs. B., aged 61 years, was a widow. One brother had died of heart disease. She had had no severe illnesses and physically was very active. She could climb stairs and hills, and worked in her garden without discomfort. The digestion was usually good.

One evening, she dined in the restaurant of the apartment hotel in which she lived. She was awakened at 2 o'clock the following morning by severe abdominal cramps, followed by profuse vomiting. The pain did not radiate to the arms or chest. The house physician was summoned, and greatly alarmed her family by stating that the symptoms were due to a heart attack resulting from acute coronary obstruction. Later in the morning, she was seen by her family doctor, who found her very weak but free from pain. The systolic blood pressure, which was usually about 125, had fallen to 110 mm. Hg. There was no fever. She remained in bed for several days and when I saw her two weeks later, felt very well.

Examination at that time showed slight sclerosis of the retinal arteries, but no thickening of the peripheral vessels. The heart was not enlarged either on per-

cussion or on fluoroscopic examination. The rhythm was regular. The sounds were of moderate intensity. There was a faint systolic blow at the apex and at the aortic area. The blood pressure was 142 mm. Hg systolic; 86 diastolic. The aorta was not dilated and its pulsations were quite vigorous. The electrocardiogram showed left axis deviation, but no other changes. In short, there were no signs of cardiovascular disease except for the moderate amount of arteriosclerosis, to which the patient, at her age, was entitled. It was thought that the attack of abdominal pain and vomiting was probably due to food poisoning. On further inquiry, it was found that three other women, who had eaten the same table d'hôte dinner in the same restaurant on the same evening were similarly affected, though they were less violently ill. The patient has been perfectly well during the past six months.

In this case, then, the symptoms of a gastrointestinal upset were attributed to acute coronary obstruction. Detailed examination revealed no evidence of heart disease, and the subsequent course has borne out the impression that the attack was not of cardiac origin.

There are mild and atypical cases, many of which are undoubtedly overlooked. A sense of substernal oppression, a mild twinge of pain, a paroxysm of dyspnea, an aching sensation in the arm or a sudden feeling of great weakness may indicate acute obstruction of a coronary twig. There may be slight fever and leucocytosis. The inference that such symptoms truly represent a thrombotic closure is often borne out by serial electrocardiographic studies in which successive changes appear in the records; or by the occurrence, months or years later, of a more severe and perhaps fatal attack. A group of such cases has recently been reported in detail.<sup>21</sup> An illustrative instance is as follows:

#### CASE REPORT

Mr. W., aged 66 years, was a business executive. One brother had died at the age of 60, of heart disease. He had never been seriously ill, nor had there been any cardiac symptoms.

The present illness began two weeks before his visit. While playing golf, he suddenly experienced a sense of pressure over the sternum, but no pain. This lasted ten or fifteen minutes, and he was able to finish the round. A week later, while coming out of a theater, the same sensation recurred, not severe, but lasting about an hour. He broke out into a profuse perspiration. On the following day, while in bed, he noted tingling in the left arm and substernal pressure, again lasting about an hour, and accompanied by sweating about the head, neck and chest. He recalled that he was obliged to change into a fresh pair of pajamas. A similar "cold sweat" occurred on the next night. At no time was there any pain, and he went to business regularly.

On examination, the patient appeared to be at least ten years younger than his stated age. The heart, by percussion, was moderately enlarged to the left. The rhythm was regular; the rate 68. The sounds were quite weak, but no gallop rhythm was heard. The blood pressure was 130 mm. Hg systolic; 86 diastolic. On fluoroscopic examination, cardiac enlargement was confirmed, and the aortic knob was found to be prominent.

An electrocardiogram was made by another physician ten days after the onset of symptoms. This showed regular sinus rhythm and slight left axis deviation. The T-wave was inverted in Lead I, and upright in Leads II and III. Another record, taken three days later, showed striking changes. T<sub>1</sub> was now upright. There

was slight elevation of the R-T interval in Lead I, and marked elevation in Lead II. There was no disturbance in conduction.

It was thought that the patient had had occlusion of a small coronary branch, and that the sense of substernal pressure and sweating appeared as substitution symptoms in place of pain. He was kept in bed for three weeks. There was no recurrence of discomfort. During the following four months, numerous electrocardiograms were taken.  $T_1$  became progressively higher and the elevation of the R-T interval in Leads I and II disappeared. These successive changes in the electrocardiograms were due, it was believed, to alteration in the state of the myocardium, associated with healing of a small myocardial infarct.

This case exemplifies one of the mild forms of coronary thrombosis without pain, in which a sense of substernal oppression was accompanied and followed by profuse sweating. Recovery was rapid, but the successive changes in the electrocardiogram afforded definite evidence of injury to the heart muscle.

Coronary thrombosis may cause almost instantaneous death, probably due to fibrillation of the ventricles. Some patients live for a few hours, others for days, months or years. Following recovery from an acute attack, life may terminate gradually, with signs of cardiac insufficiency, or suddenly, due to a fresh obstructive lesion. Occasionally, the heart wall, weakened by a large area of necrosis, ruptures. If the infarct heals and is replaced by an extensive fibrotic scar, an aneurysm of the ventricle may develop.<sup>22</sup>

In a series of 287 cases analyzed by Conner and Holt,<sup>23</sup> the immediate mortality in the first attack was 16 per cent. Among the patients in their group having two or more attacks, the time interval between the first and second attack was less than one year in half the cases. One patient remained in good health for seventeen years and died in a second attack eighteen years after the first. Mild initial symptoms and a rapid rate of recovery tend to indicate a favorable immediate outcome. But in any given instance, it is extremely difficult to prognosticate as to the liability to recurrence, or to estimate the probable expectancy of life.

A presentation such as this is necessarily fragmentary and incomplete. I shall take comfort from the words of Oliver Wendell Holmes,<sup>24</sup> who, in a lecture delivered at the Harvard Medical School in 1867, gave this advice to the junior members of the faculty: "Do not fret over the details you have to omit; you probably teach altogether too many as it is."

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# THE OPENING SNAP (*CLAQUEMENT D'OUVERTURE DE LA MITRALE*) IN MITRAL STENOSIS, ITS CHARACTERISTICS, MECHANISM OF PRODUCTION AND DIAGNOSTIC IMPORTANCE\*†

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IN MOST patients with mitral stenosis a characteristic snapping or clicking sound occurs shortly after the second heart sound. It is sometimes audible over the entire precordium. It is usually heard best in the fourth left interspace and occasionally may be louder in this position than either the first or second sound. In spite of the fact that the sound has been clearly described a number of times, it seems never to have gained the recognition merited by its diagnostic significance. It has been confused by most writers either with reduplication of the second heart sound or with gallop rhythm. Reduplication of the second sound is frequently present in mitral stenosis but has practically no diagnostic importance, since it is often found in undamaged hearts and in various types of heart disease other than mitral stenosis. It is questionable whether gallop rhythm ever occurs in the presence of well-developed mitral stenosis. The sound, however, to which we wish to recall attention does help to produce a *grouping* of sounds not very different from that of protodiastolic gallop rhythm. However, it resembles gallop rhythm in no other of its physical characteristics and may be readily differentiated from it.

Duroziez<sup>1</sup> in 1862 gave the first recognizable description of this third sound as a part of the pathognomonic sound rhythm of mitral stenosis (which he represented by the syllables *ffout-ta-ta-rou*), but he, and later Potain<sup>2</sup> ascribed it to asynchronism in aortic and pulmonic closure. Guttman<sup>3</sup> was the first to recognize that the sound is not due to reduplication at the base. He made the important suggestion that it originates at the stenosed mitral orifice itself; although he stated erroneously that it is most clearly heard over the lower part of the sternum or near the apex of the heart. In 1881 the sound was described for the first time in the English literature by Sansom,<sup>4</sup> who adopted Guttman's view that it is produced at the mitral orifice. He believed that the cause of the sound is tension on the "mitral curtains." Sansom invented the term "reduplication of the second sound at the apex," which unfortunately persists.

In 1888, Rouches,<sup>5</sup> whose interest had been stimulated by Potain, pub-

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lished a thesis on the subject. He characterized the sound as a sharp snap heard in mitral stenosis with or without associated insufficiency, coming shortly after the second sound and marking the beginning of the diastolic rumble. He called the sound *Le claquement d'ouverture de la mitrale*, stating that Potain had used this term in his teaching.\* Among Rouches' conclusions were the following: (1) the active cause of the *claquement d'ouverture de la mitrale* is stretching of the stenosed valves by the pressure of blood unable to flow freely from the auricles; (2) the sound does not occur if the valve leaflets do not retain some suppleness and ability to snap when stretched; (3) the sound therefore denotes the presence of pronounced but not extreme stenosis. Following the contributions of Guttman, Sansom, and Rouches, other papers appeared<sup>6, 7</sup> but added nothing of importance to the observations of these investigators. In 1905 and again in 1912, Gallavardin<sup>8, 9</sup> discussed this sound and attributed it to the effect of a shock-like wave, initiated by aortic closure. He assumed further that this wave traveled downward and struck against a stenosed but open mitral valve. In his second paper, the physiological third heart sound was attributed to the shock-like wave striking a normal open mitral valve. The differences in quality of the sounds were regarded as due merely to the differences in the physical properties of the normal and stenosed valves.

Heart sound registration methods offer an excellent opportunity to study this sound, since it is easily recorded. A search of the literature, however, reveals the fact that very little work has been done in this field. Lewis<sup>10</sup> noted a gap between the second sound and the beginning of the diastolic murmur. Wilson and Wishart<sup>11</sup> also observed a pause between the second sound and the beginning of the diastolic murmur which gave rise to a triple rhythm. Groedel<sup>12</sup> has recently referred to a "splitting" of the second sound and states that the diastolic murmur begins with large vibrations which one can hear as a third sound. These statements can be confirmed by sound registration methods in certain cases of mitral stenosis, but all these writers overlook the snapping sound pointed out by earlier observers. It is true that there is a gap between the second heart sound and the beginning of the diastolic murmur which is revealed by sound tracings if the recording apparatus is sufficiently damped. It is likewise true that the tracings frequently show the murmur of mitral stenosis to be initiated by a series of vibrations of relatively large amplitude. The characteristic third sound of mitral stenosis, however, is neither a part of the second sound nor a part of the murmur. It disturbs the quiet of what would otherwise be an auscultatory gap between the second sound and the murmur.

Recently Mozer and Duchosal<sup>13</sup> have published sound tracings in which they have called attention to the snap (*bruit de rappel*). These workers

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\*Apparently Potain had come to this conclusion after publishing the paper in 1875 referred to above.

adopted Gallavardin's hypothesis with respect to the mechanism of production of the sound and ascribed not only the physiological third heart sound but also reduplication of the second sound to the same mechanism. These views will be discussed later.

*Nomenclature.* Of the various designations which have been used to call attention to this characteristic sound in mitral stenosis, Rouches' *claquement d'ouverture de la mitrale* and the corresponding term "opening snap" used by Thayer<sup>11</sup> are the most acceptable. In the earlier part of our work, we were unwilling to adopt this term on the ground that it implied a mechanism of production of the sound which was unproved. Our studies of this mechanism, however, support the view held by the earlier writers that the sound is due to an opening snap of the mitral valve, thus warranting retention of the term. The designation *bruit de rappel* which has been used by certain French writers, although picturesque, has little significance and should be discarded.

*Material and Methods of Sound Registration.* During the past three years we have made clinical and sound registration studies in 60 cases of mitral stenosis. Some of the cases have been followed throughout most of this time, others for shorter periods. The apparatus which has been used for recording sound includes a three-stage transformer coupled amplifier,<sup>\*</sup> the Western Electric transmitter and output receiver. In the early part of the work, the optical apparatus devised by Wiggers was used.<sup>†</sup> Because of the limitations of the Wiggers apparatus in recording high-pitched sounds and its imperfect damping quality, at least so far as our ability to use it is concerned, it was regarded as unsuitable to record the snap satisfactorily and to display its time relationships. Consequently the rubber cement membrane and reflecting mirror were attached over the outlet of the output receiver, making possible the use of a smaller membrane with a higher vibration frequency and quicker damping. With this modification,<sup>‡</sup> which eliminates one part of the apparatus and therefore one possibility for distortion of sound, the snap is easily recorded and because the sounds are quickly damped their time relationships are clearly displayed. Waves of low frequency are not recorded with as great amplitude as with the Wiggers device, or with the electrocardiographic string, but for our present purposes this is unimportant.

#### THE FREQUENCY OF THE OPENING SNAP AND ITS CHARACTERISTICS

The sound is audible in the majority of cases of mitral stenosis. We were able to elicit it, both by auscultation and by sound registration

<sup>\*</sup>The amplifier has a frequency characteristic adapted for heart sounds. It was constructed for us by Professor Charles Weyl of the Moore School of Electrical Engineering, University of Pennsylvania.

<sup>†</sup>Numerous tests were made to determine the adequacy of this apparatus. These have been previously mentioned.<sup>12</sup>

<sup>‡</sup>This modification of the method will be described by one of us (Margolies) in a separate publication.

methods, in 19 of 34 consecutive cases in which this valve lesion was diagnosed. Its occurrence does not seem to be materially influenced by the presence or absence of associated lesions. Gallavardin<sup>9</sup> failed to elicit the snap when aortic regurgitation was present, and Mozer and Duchosal<sup>13</sup> also failed to find it in two such cases. These authors, therefore, state that aortic regurgitation prevents the occurrence of the snap. This observation was believed by them to have great significance with respect to the mechanism of production of the snap. As a matter of

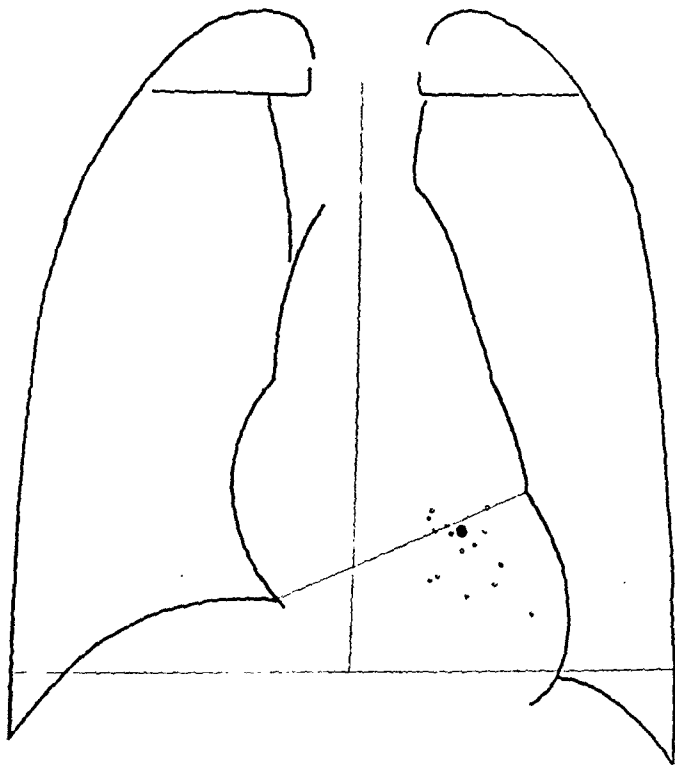


Fig. 1.—The relation of the position of maximum audibility of the opening snap to the basal diameter and the left border of the heart. (See text for description of method.) The large dot represents this position in the patient from whom the orthodiagram was made. The small circles represent this relationship in fifteen other cases. The drawing does not take into account the differences in size, shape and position of the heart in these fifteen cases. For example, the lowest circle was taken from the orthodiagram of a patient with a very large heart in whom the snap was not so close to the apex as its position in this drawing would suggest. The point of maximum audibility is never basal or apical.

fact, the occurrence of the snap is not prevented by the presence of aortic regurgitation. We have studied 4 cases with both mitral stenosis and aortic regurgitation in which the snap could be heard and recorded.

*Quality and Intensity.* The sound is always short, and usually high-pitched, having a snapping or clicking quality. Its intensity varies. It is frequently loud enough to be audible over the entire precordium. Sometimes it is less distinct and is heard over a limited area only.

*Area of Maximum Audibility.* The area over which the sound is heard best is usually located in the fourth interspace, just inside the left border

of the heart. Occasionally it is heard best in the third interspace. Fig. 1 is a diagram made in the attempt to illustrate the relation which this point bore to the cardiac silhouette in 16 cases. These data were obtained by determining the position of maximum loudness of the sound by auscultation with a stethoscope. The position was marked by strapping a small piece of lead over it. Its relation to the cardiac shadow was then determined by fluoroscopy. The latter was found to be from 1.5 to 4.5 cm. inside the left border and usually from 0.5 cm. above to 2.5 cm. below the so-called basal diameter.\*

The area over which the snap is heard best is slightly above and to the right of the area over which the characteristic diastolic murmur of mitral stenosis is usually most clearly audible. This auscultatory finding is supported by a comparison of the relative amplitudes of the vibrations in sound tracings taken over these two areas (Fig. 2 *A* and *B*).

*Transmission.* The opening snap does not seem to be transmitted in any particular direction, but if it is loud enough to be heard at a distance, it is sometimes more distinct over the aortic than over the pulmonic area.

*Time Relation to the Second Heart Sound.* In our cases the snap usually occurred 0.06 to 0.11 second after the beginning of the second sound. The shortest interval recorded was 0.03 second (after ac-

TABLE I  
EFFECT OF CHANGE OF CARDIAC RATE ON DURATION OF SECOND SOUND—  
OPENING SNAP INTERVAL

| CASE   | INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS | DURATION OF PRECEDING HEART CYCLE, IN SECONDS |
|--|---|---|
| Case 1   | 0.04  | 0.62  |
| Rate accelerated by<br>amyl nitrite.                         | 0.06  | 0.67  |
|  | 0.07  | 0.76  |
|  | 0.07  | 0.79  |
| Representative meas-<br>urements during re-<br>covery stage. | 0.08  | 0.80  |
|  | 0.08  | 0.83  |
|  | 0.08  | 0.85  |
|  | 0.09  | 0.87  |
|  | 0.09  | 0.90  |
|  | 0.09  | 0.95  |
|  | 0.09  | 0.97  |
| Case 2   | 0.08  | 0.78  |
| 3/14/30  | 0.08  | 0.80  |
|  | 0.09  | 0.88  |
| 5/31/30  | 0.10  | 0.92  |
|  | 0.10  | 0.96  |
|  | 0.10  | 0.96  |

\*The basal diameter is a line drawn from the right cardiophrenic junction to the point on the left border between the left auricular appendage and the left ventricle.

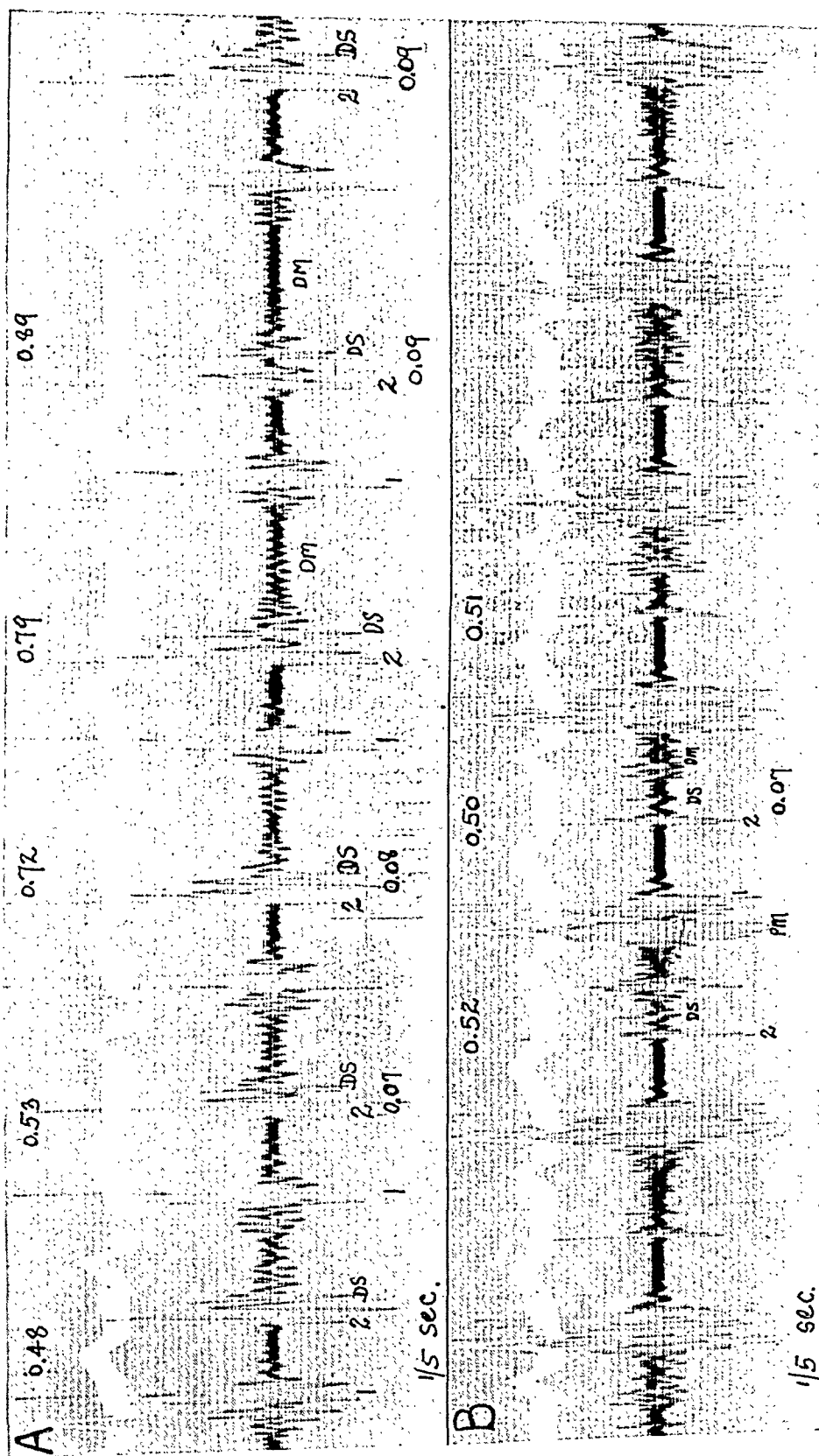


Fig. 2.—Upper tracing (A) recorded in third interspace shows a loud snap (DS) and insignificant diastolic murmur (DM). The effect of sinus arrhythmia on the time relationship of the snap to the second sound is shown by comparison of the first two and the last two beats. The lower tracing (B) recorded in the fourth interspace shows the snap (DS) to be insignificant but the murmur prominent. The gaps between the second sound and the snap, and between the snap and the beginning of the typical murmur of well-developed mitral stenosis are clearly shown.

celerating the heart action by means of amyl nitrite). The longest was 0.19 second (after a very long preceding heart cycle in a case of auricular fibrillation with a widely split second sound). Short intervals are illustrated in Fig. 3 *A* and *B*, and long intervals in Figs. 4 and 7.

Cardiac rate appears to be a factor which affects the duration of the interval. This is evidenced by the fact that in a given individual if sound tracings are obtained showing substantial differences in cardiac rate, differences are found in the duration of the interval between the

TABLE II

DURATION OF SECOND SOUND—OPENING SNAP INTERVALS IN PATIENTS WITH SINUS RHYTHM

| CASES         | INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS | DURATION OF PRECEDING HEART CYCLE, IN SECONDS |
|---------------|---|---|
| Case 1. C. D. | 0.06  | 0.54  |
|               | 0.06  | 0.53  |
|               | 0.06  | 0.58  |
| Case 2. C. S. | 0.07  | 0.66  |
|               | 0.07  | 0.61  |
| Case 3. S. H. | 0.06  | 0.76  |
|               | 0.06  | 0.76  |
| Case 4. S. S. | 0.10  | 0.78  |
|               | 0.10  | 0.78  |
|               | 0.09  | 0.77  |
|               | 0.10  | 0.76  |
| Case 5. S. G. | 0.10  | 0.83  |
|               | 0.10  | 0.81  |
|               | 0.10  | 0.83  |
| Case 6. D. P. | 0.09  | 0.95  |
|               | 0.10  | 0.98  |
| Case 7. R. M. | 0.08  | 1.04  |
|               | 0.07  | 0.95  |
|               | 0.07  | 1.00  |
| Case 8. J. W. | 0.08  | 0.90  |
|               | 0.08  | 0.96  |
|               | 0.10  | 1.00  |
|               | 0.10  | 1.08  |
| Case 9. T. R. | 0.06  | 0.93  |
|               | 0.07  | 0.99  |
|               | 0.06  | 1.00  |
|               | 0.08  | 1.00  |
|               | 0.07  | 1.00  |
|               | 0.08  | 1.03  |
|               | 0.08  | 1.10  |
|               | 0.08  | 1.14  |
|               | 0.08  | 1.17  |
|               | 0.08  | 1.22  |

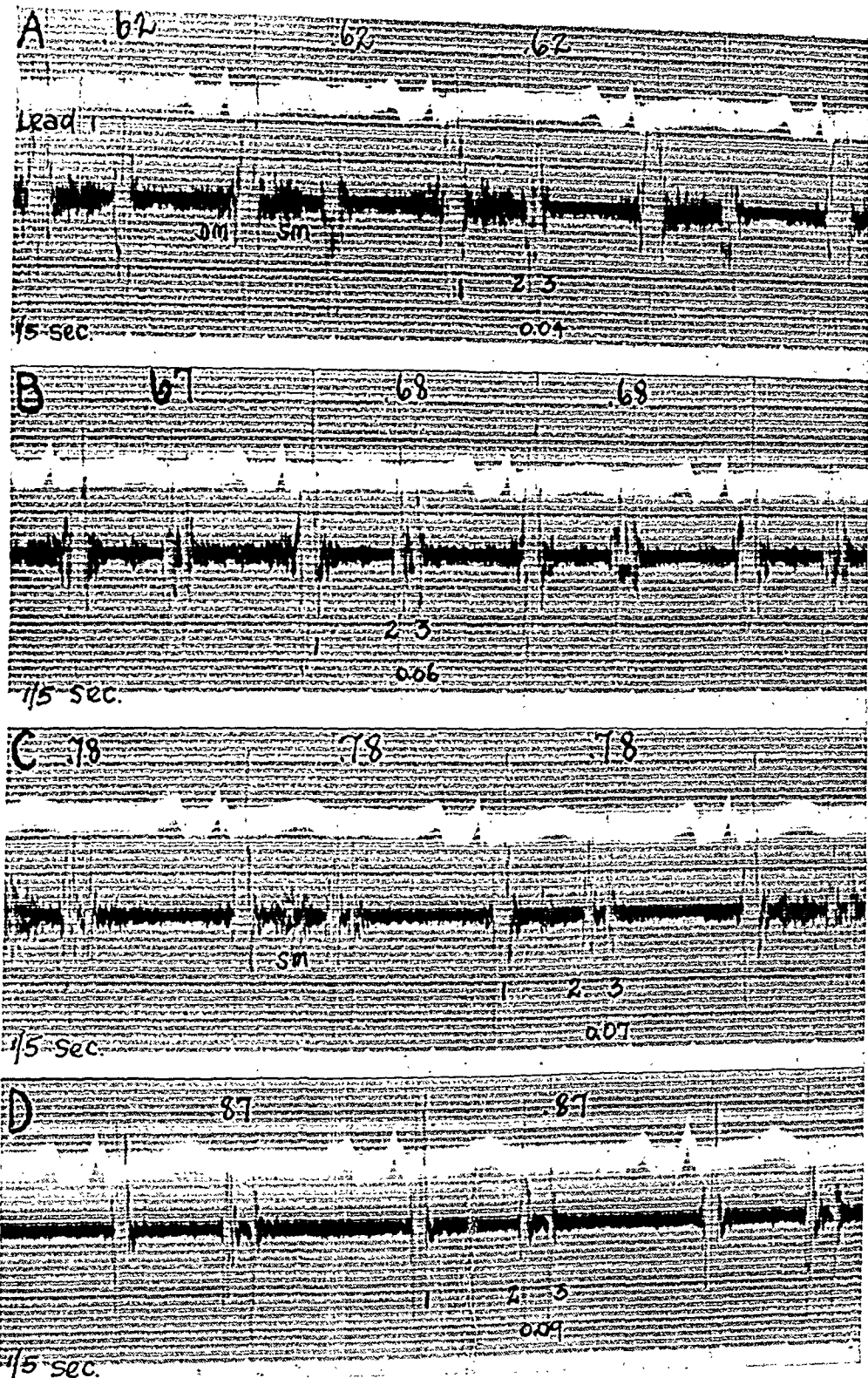


Fig. 3.—Mitral stenosis, opening snap. The effect of change of cardiac rate on the interval between the second sound and the opening snap. The heart cycle length of 0.62 second shown in A was produced by amyl nitrite, the cycle length of 0.68 second in B by excitement (being told she was to receive amyl nitrite), the cycle length of 0.78 second in C occurred during the recovery from amyl nitrite, and the cycle length of 0.87 second shown in D was recorded before the patient was told that she was to receive amyl nitrite. Tracings with time relationships similar to those of D were obtained after recovery from amyl nitrite. The interval between the second sound and the opening snap varied from 0.04 to 0.09 second becoming longer as the rate slowed.

beginning of the second sound and the snap. The changes tend to be in the same direction; as the length of the cardiac cycle increases, the duration of the interval increases (Table I and Fig. 3).

The above statements apply only to the variations observed in individuals. When the time relations in a series of cases were compared, no satisfactory correlation was observed between cardiac rate and the interval (Table II) except that all cases with rapid rate exhibited a short interval.

It is obvious, therefore, that other factors besides cardiac rate must be of importance in determining the time relationship of the snap to the second sound. The evaluation of such factors would be difficult. It is well known that the position of the second heart sound is determined by intraventricular and arterial pressure relationships. When intraventricular pressure falls below arterial pressure, the semilunar valves close and produce the second sound. As a rule the second sound occurs approximately at the end of the T-wave of the electrocardiogram, although it may come before or slightly after this event. If the snap is produced by the attempt of the stenosed mitral valve to open, as was suggested by Guttman, Sansom and Rouches, its time with respect to early ventricular diastole must be determined by the instant that left intraventricular pressure falls below left intra-auricular pressure. Thus since it is probable that the time incidence of both sounds depends on pressure relationships, in the one case of the ventricles and great vessels and in the other of the left auricle and left ventricle, it would seem that variation of the interval is possible under diverse circumstances.

The opening snap is heard in cases of auricular fibrillation quite as well as when the auricles are beating normally. In most cases of fibrillation there are changes in the time relation of the snap to the second sound from beat to beat which seem to depend on the duration of the preceding heart cycle (Fig. 4 and Table III). Variations of intervals are also found in association with other forms of irregularity of rhythm such as sinus arrhythmia (Fig. 2 A and Table II, Cases 8 and 9). After a short preceding heart cycle, the snap usually falls nearer the second sound. After a long period it usually falls later, and the interval separating it from the second sound is correspondingly greater.\* These differences may be as great as 0.05 second. Very slight variations of the interval may also occur during regular rhythm, depending on the phase of respiration.

\*Occasionally exceptions to this rule are found. In some cases beats falling early show a longer interval between the second sound and the snap. These exceptions apparently depend on early closure of the semilunar valves in relatively premature and feeble beats, leaving a larger share of the relaxation process than usual to be accomplished after semilunar closure. The relationship in comparatively premature beats between early semilunar valve closure and delay in the snap is shown in Fig. 5 and Table III (Case 7). It is also of interest that, in general, the intervals tend to be longer when auricular fibrillation is present than when the rhythm is normal. For this phenomenon, we have no explanation.



TABLE III

COMPARISON IN AURICULAR FIBRILLATION BETWEEN HEART CYCLE LENGTH AND  
DURATION OF SECOND SOUND—OPENING SNAP INTERVALS

| CASE          | INTERVAL BETWEEN BEGINNING<br>OF SECOND SOUND AND OPEN-<br>ING SNAP, IN SECONDS | DURATION OF PRECEDING HEART<br>CYCLE, IN SECONDS |
|---------------|---|--|
| Case 1. A. F. | 0.08  | 0.51   |
|               | 0.09  | 0.53   |
|               | 0.10  | 0.76   |
|               | 0.10  | 0.78   |
|               | 0.11  | 0.89   |
|               | 0.11  | 0.98   |
|               | 0.12  | 1.32   |
| Case 2. H. O. | 0.07  | 0.54   |
|               | 0.08  | 0.64   |
|               | 0.09  | 0.72   |
|               | 0.10  | 0.84   |
|               | 0.11  | 0.96   |
|               | 0.12  | 1.00   |
|               | 0.12  | 1.08   |
| Case 3. C. H. | 0.09  | 0.73   |
|               | 0.10  | 0.79   |
|               | 0.10  | 0.80   |
|               | 0.11  | 0.82   |
|               | 0.10  | 0.91   |
|               | 0.11  | 0.92   |
|               | 0.12  | 1.15   |
|               | 0.11  | 1.39   |
|               | 0.11  | 1.51   |
| Case 4. J. M. | 0.12  | 1.61   |
|               | 0.10  | 0.78   |
|               | 0.11  | 0.80   |
|               | 0.11  | 0.81   |
|               | 0.10  | 0.83   |
|               | 0.11  | 1.00   |
|               | 0.11  | 1.03   |
|               | 0.11  | 1.12   |
|               | 0.11  | 1.14   |
|               | 0.11  | 1.16   |
|               | 0.11  | 1.20   |
|               | 0.11  | 1.26   |
| Case 5. J. N. | 0.06  | 0.55   |
|               | 0.07  | 0.65   |
|               | 0.08  | 0.70   |
|               | 0.08  | 0.73   |
|               | 0.09  | 0.74   |
|               | 0.09  | 0.75   |
|               | 0.09  | 0.76   |
|               | 0.08  | 0.85   |
|               | 0.09  | 0.92   |
|               | 0.09  | 1.00   |
|               | 0.09  | 1.15   |
|               | 0.10  | 1.30   |
|               | 0.10  | 1.45   |
|               | 0.11  | 1.54   |
|               | 0.11  |  |

TABLE III—CONTINUED

| CASE          | INTERVAL BETWEEN BEGINNING<br>OF SECOND SOUND AND OPEN-<br>ING SNAP, IN SECONDS | DURATION OF PRECEDING HEART<br>CYCLE, IN SECONDS |
|---------------|---|--|
| Case 6. M. T. | 0.07  | 0.48   |
|               | 0.08  | 0.66   |
|               | 0.08  | 0.71   |
|               | 0.08  | 0.74   |
|               | 0.09  | 0.77   |
|               | 0.08  | 0.78   |
|               | 0.09  | 0.82   |
|               | 0.09  | 0.85   |
|               | 0.09  | 0.93   |
|               | 0.10  | 0.95   |
|               | 0.09  | 1.31   |
|               | 0.11  | 1.46   |
| Slower rate   | 0.09  | 0.74   |
|               | 0.09  | 1.02   |
|               | 0.09  | 1.18   |
|               | 0.10  | 1.31   |
|               | 0.10  | 1.34   |
|               | 0.10  | 1.35   |
|               | 0.11  | 1.60   |
|               | 0.10  | 1.69   |
|               | 0.10  | 1.78   |
|               | 0.10  | 1.80   |
| Case 7. E. M. | 0.10  | 0.49   |
|               | 0.10  | 0.53   |
|               | 0.11  | 0.54   |
|               | 0.10  | 0.62   |
|               | 0.09  | 0.75   |
|               | 0.09  | 0.79   |
|               | 0.10  | 0.86   |
|               | 0.10  | 0.88   |
|               | 0.11  | 1.16   |
|               |   |  |

*Time Relation of Snap to Diastolic Murmur.* According to both Guttman<sup>3</sup> and Rouches,<sup>5</sup> the snap marks the beginning of the diastolic murmur of mitral stenosis. Although this is the usual impression obtained by auscultation, sound records sometimes show the snap to precede the beginning of the murmur by an appreciable, though very short, interval (Fig. 2 B). This can occasionally be detected on auscultation.

The "Auscultatory Gap." In cases of well-developed mitral stenosis which fail to show the snap, it is possible to record the auscultatory gap described by Lewis,<sup>10</sup> and Wilson and Wishart,<sup>11</sup> i.e., the interval between the second sound and the beginning of the murmur. This gap, which is clearly perceptible to the ear, has considerable value as a diagnostic sign of mitral stenosis. It is especially useful in differentiating a diastolic murmur arising at the mitral valve from one arising at either of the semilunar valves. The onset of the former is separated from the

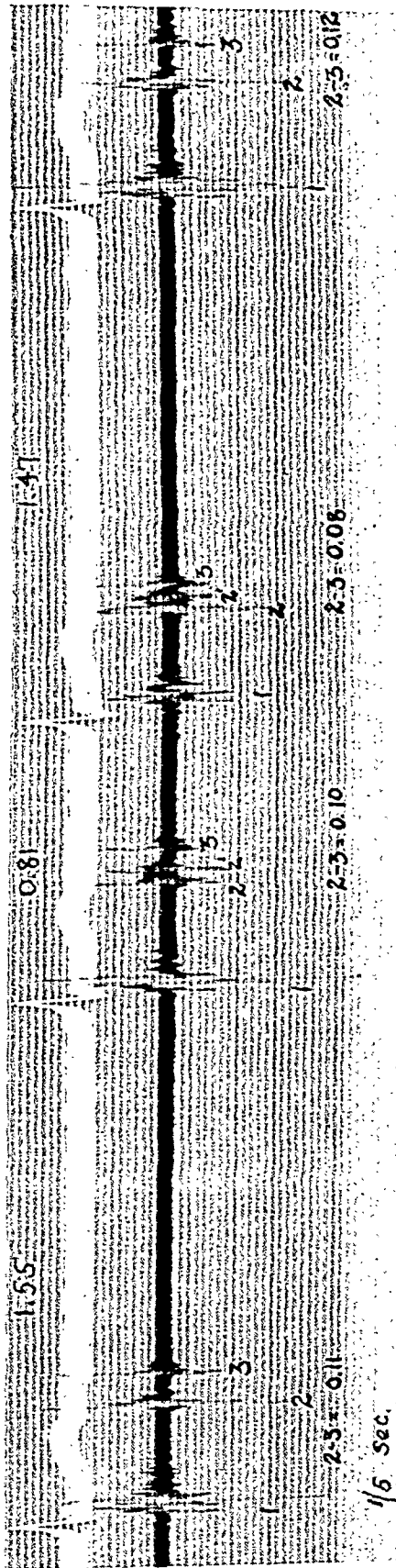


Fig. 4.—Mitral stenosis, auricular fibrillation, phasic reduplication of the second sound and opening snap. The second and third beats show reduplication of the second sound while the first and fourth fall to show reduplication. The snap is recorded in all. The presence or absence of reduplication in this case depended on the phase of respiration. In the third beat which falls after a shorter rest period, the interval between the second sound and the opening snap is shorter than in the other beats.

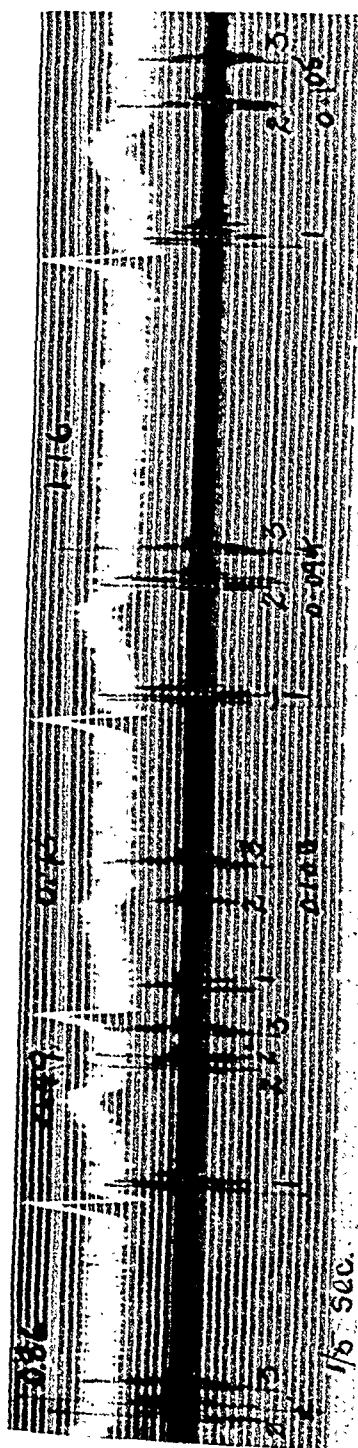


Fig. 5.—Mitral stenosis, auricular fibrillation, opening snap, phasic reduplication of the second sound. In the second beat, which is relatively premature, both the second sound and the snap fall earlier with respect to the end of the T-wave than in the less premature beats. The second sound has changed its position more than the snap, thus causing the interval between them to be greater than in less premature beats. This case constitutes the only exception we have encountered to the general rule that the interval varies in the same direction as the length of the preceding heart cycle.

second sound by this gap.\* The murmur of either aortic or pulmonic regurgitation is continuous with the second sound, unless dynamic events on the two sides are asynchronous. Thus in one case with aortic regurgitation and bundle-branch block it was possible to detect on auscultation and to demonstrate by means of sound tracings a gap between the second sound and the aortic diastolic murmur.

*Variation in the Sound Intensity of the Snap.* The sound intensity of the snap may vary from time to time in a given individual, a fact first pointed out by Rouches.<sup>5</sup> In one of our patients, for example, the sound was not heard when she was sitting quietly (heart rate 70 beats per minute). After she had walked up and down the room several times it became distinctly audible, though not loud (heart rate 84 beats per minute). When the rate was still further increased (100 beats per minute), the snap became quite loud. It then decreased in intensity and finally disappeared as the heart rate declined. As a rule, the sound is more distinct when the patient is in the recumbent position. The reason for these differences is not known; possibly they depend on the level of intra-auricular pressure at the beginning of ventricular diastole, and the speed of ventricular relaxation.

*Relation to Reduplicated Second Sounds.* Rouches<sup>5</sup> was apparently the first to observe that the *claquement* and splitting of the second sound both may be present in the same heart cycle. Despite the fact that this is a common finding, readily confirmed by means of sound tracings, other writers do not mention it. When splitting of the second sound and the opening snap occur in the same heart cycle, it is of interest to note the time relations of the two components of the second sound to the opening snap. This can be studied under a variety of circumstances. Among cases with normal intraventricular conduction showing respiratory phasic splitting of the second sound, in which the doubling tends to occur during the inspiratory phase of the respiratory cycle, the snap maintained its time relationship with the first component of the split sound.†

\*Wilson and Wishart<sup>11</sup> state that the diastolic murmur of mitral stenosis is sometimes continuous with the second heart sound. We have never observed it. According to what is known of cardiodynamics, it would scarcely seem possible for a mitral diastolic murmur to be continuous with the aortic second sound. If, however, the second sound were widely split and pulmonic closure followed aortic closure, it is possible that the murmur might be continuous with the pulmonic component of the second sound. When reduplication of the second sound, the opening snap and a mitral diastolic murmur are all present, it should be possible to hear and record three short sounds followed by a murmur. The intervals between these sounds and the murmur are very short, so that registering apparatus without adequate damping records them as continuous vibrations resembling those obtained from murmurs. This point is illustrated in Fig. 9. In A, the three sounds recorded by means of the electrocardiographic string are not clearly separated and give the impression of a continuous sound. In B, in which damping is more adequate, the sounds are clearly separated.

†Katz<sup>10</sup> has found in experimental cardiodynamic studies that there is frequently appreciable asynchronism in the duration of ventricular systole on the two sides. Such asynchronism might be expected to cause splitting of either the first or the second heart sound or both. Our observations indicate that in cases of mitral stenosis with split second sounds and no electrocardiographic evidence of disturbed intraventricular conduction, aortic closure tends to precede pulmonic closure. It is, of course, entirely possible that the sequence might occasionally be reversed.

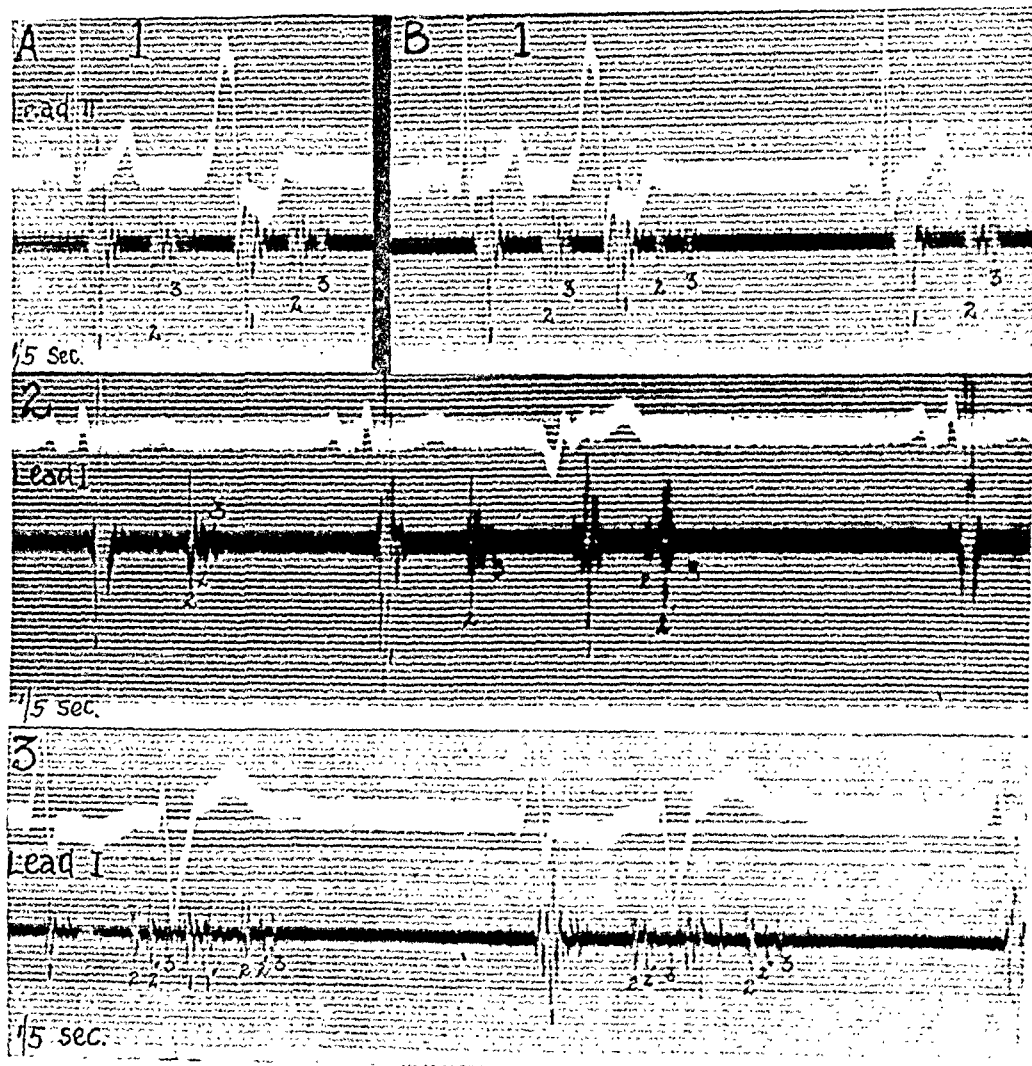


Fig. 6.—The time relations of the opening snap to the second sound in ventricular extrasystoles. In Strip 1-A, the extrasystolic second sound (2) is reduplicated, and the snap maintains its time relation with the second component. In Strip 1-B, the extrasystole is more premature, and the second component of the second sound drops out. The snap (3) cannot be related to the component of the second sound (2) recorded since the time interval is too great. Strip 2 was recorded from the same case as Strip 1 and is included to show the shape of the extrasystolic complexes in Lead I of the electrocardiogram. Strip 3 was obtained from another patient in whom, although the extrasystolic complexes differed materially from those of the first case, the main deflection was downward in Lead I. In this case the snap was invariably related to the first component of the split second sound.

The second sound is usually split both in ventricular extrasystolic beats and in the presence of bundle-branch defect.\* Studies were made in two cases exhibiting the opening snap and numerous ventricular extrasystoles with split second sounds. The main QRS deflections of the extrasystolic beats, although differing considerably in shape in the two cases were downward in Lead I and upward in Lead III in both. In one case the snap invariably maintained its time relationship to the first com-

\*Unpublished observations. It has long been known that the first sound may be split when bundle-branch block is present. King has recently ascribed diagnostic significance to this finding. The first sounds of ventricular extrasystoles also tend to be split.

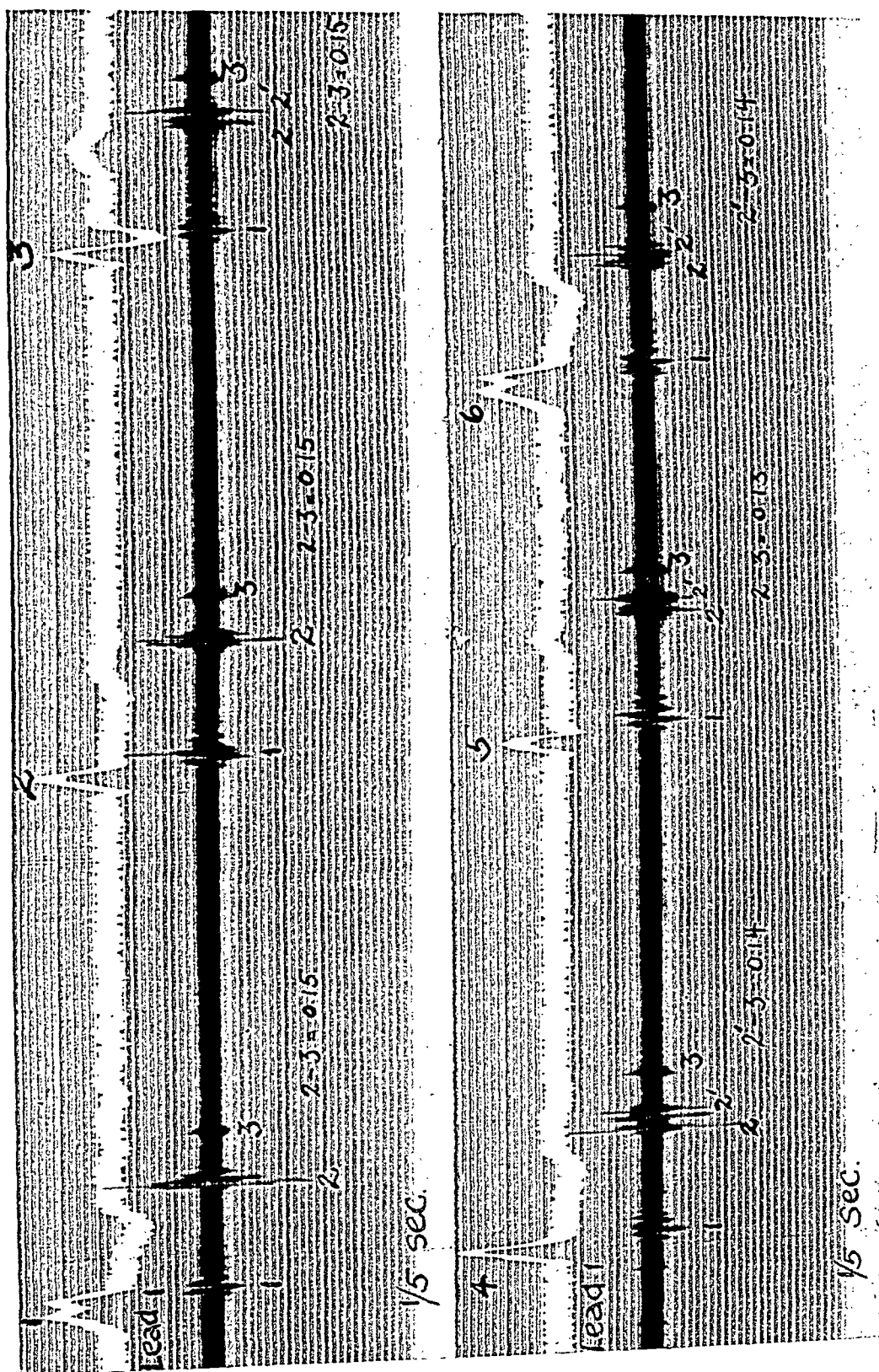


Fig. 7.—Mitral stenosis, auricular fibrillation, opening snap, various types of ventricular complexes. Four different types of beats (3, 4, 5 and 6) show splitting of the second sound (2, 2'). In beats 3 and 5, the snap (3) maintains its time relation to the first component of the split second sound and in beats 4 and 6 to the second component. In beat 1, the electrocardiogram is the same as in beat 6, yet no splitting is recorded. One component may be so faint as to fail to record or the two may be merged. This case exhibits the longest interval which we have observed between the second sound and the snap in beats with single second sounds (of which only two are shown in the figure) the second sound-snap interval varied from 0.13 to 0.15 second. In beats with split second sounds, the interval between one component of the second sound and the snap always fell within this range.

ponent and in the other case to the second component of the split second sound in the extrasystolic beats (Fig. 6). We have studied one case in which a variety of aberrant ventricular complexes was recorded (Fig. 7). Four different types exhibited splitting of the second sound. In two types, the snap maintained a constant relation to the first component of the second sound and in the other two types to the second component. One of these types of beats fulfilled the electrocardiographic criteria of bundle-branch block (Fig. 7, beats 1 and 6). According to the views of Wilson and his associates,<sup>17</sup> the block was left-sided since the main QRS deflection was upward in Lead I and downward in Lead III. In all beats of this type in which splitting of the second sound was recorded, the snap invariably maintained a significant time relationship to the second component of the split sound.\*

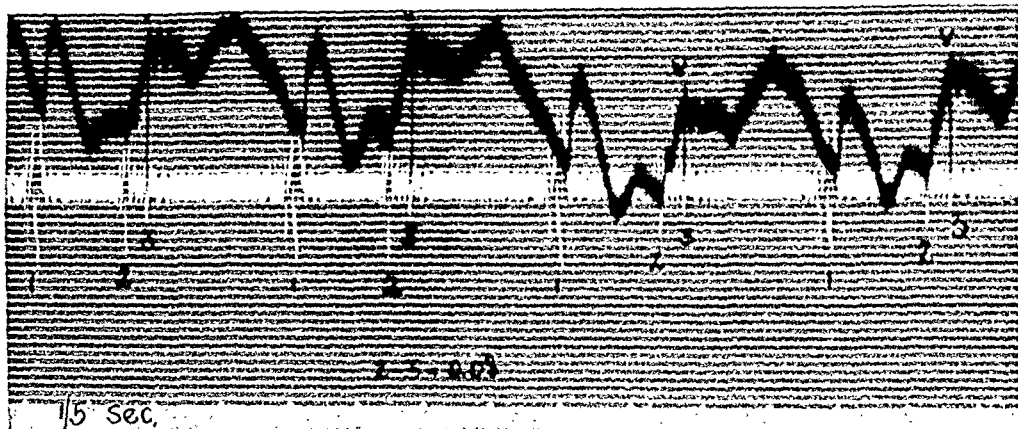


Fig. 8.—Mitral stenosis and opening snap. Sound tracing (recorded with electrocardiographic string) and optically recorded jugular phlebogram. The snap (3) and the summit of the V-wave are practically simultaneous.

*Relation to Jugular Pulse.* The comparison of the time relations of the opening snap and the jugular pulse, recorded without parallax, was made in eight cases. These tracings show that the opening snap occurs approximately synchronously with the summit of the V-wave (Fig. 8), provided the second sound is not reduplicated.

The summit of the V-wave is supposed to mark the end of the isometric relaxation phase and the beginning of right ventricular filling. This relationship held as constantly in the cases with auricular fibrillation as in those with normal rhythm, despite the fact that in the former the time interval between the beginning of the second sound and the snap varied from beat to beat. When this occurred the interval between the second

\*The time relationships of the snap to split second sounds in ventricular extrasystoles and bundle-branch block have a bearing on the question as to the spread of the excitatory process in these conditions. This will be considered in connection with other evidence in a subsequent publication. It might be said, however, that the evidence presented here supports the views of Wilson and his associates with respect to the side of origin of bundle-branch block and those ventricular extrasystoles which have electrocardiographic complexes similar to those of bundle-branch block. It is questionable, however, as to whether a sharp dividing line between right and left ventricular extrasystoles can be established on the basis of the direction of the main deflections in Leads I and III.



sound and the V-wave showed the same variation. In two cases studied by this method, a phasic respiratory incidence of splitting of the second sound was present. In both these cases, when the second sound was single, the time of the snap and the summit of the V-wave coincided. This result was the same as that obtained in the other six cases. When

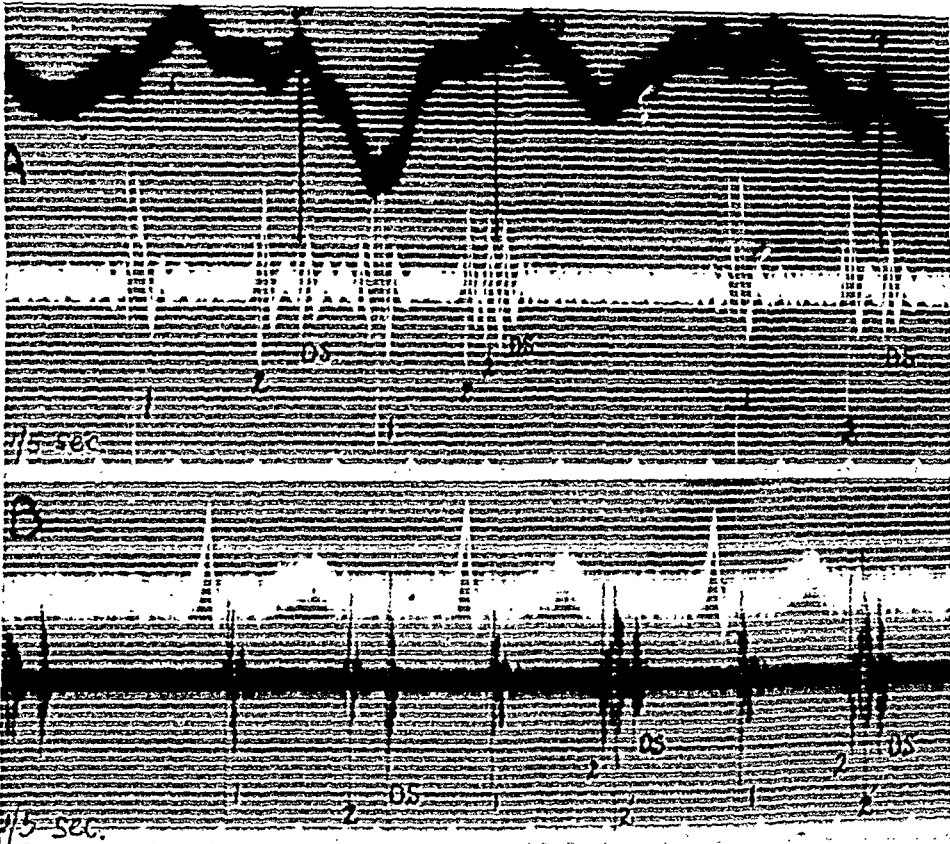


Fig. 9.—Mitral stenosis, auricular fibrillation, phasic (respiratory) reduplication of the second sound, opening snap. In A, the time relations of the jugular pulse and sounds recorded by means of the electrocardiographic string are compared. In the first and third beats, in which the second sound is single, the snap falls at the summit of the V-wave. In the second beat, there is reduplication of the second sound. (Due to the poor sensitivity and damping qualities of the string, the two elements of the reduplicated second sound and the opening snap resemble a murmur.) Note how far the summit of the V-wave in this beat lags behind the snap. The time interval between the second component of the second sound and the V-wave is practically identical with the interval between the single second sounds of the first and third beats and the summit of the respective V-waves. This indicates that the second component of the split second sound is due to pulmonic closure. The sound tracing in B was recorded from the same position (fourth left interspace) by means of a very small rubber cement membrane sensitive to waves of high frequency and with excellent damping. When reduplication of the second sound is present, the three sounds in rapid succession are clearly recorded.

the second sound was split, however, pulmonic closure lagging after aortic, the snap tended to precede the summit of the V-wave (Fig. 9).

It would appear, therefore, that reduplication of the second sound tends to be accompanied by a similar degree of asynchronism between the summit of the V-wave, which is a right-sided phenomenon, and the opening snap, which is left-sided in origin.

*Relation to Excursion of Left Ventricular Border.* The relation of the snap to excursion of the left ventricular border was studied in six cases. Simultaneous electrocardiograms and roentgen kymograms\* of the left ventricle were made. Simultaneous electrocardiograms and sound tracings were also taken in the same individuals, with care to avoid

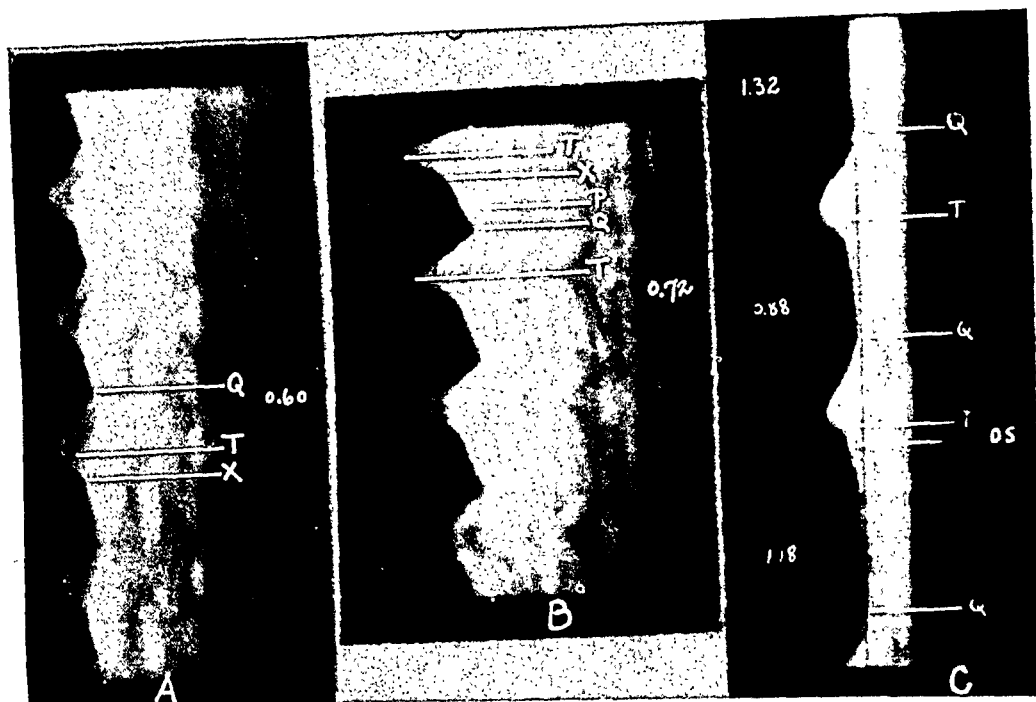


Fig. 10.—Roentgen kymograms of the left ventricle in three cases of mitral stenosis with opening snap. The dark shadow is produced by the heart. The tracing should be read from above downward. The letter *P* identifies the position of the beginning of the P-wave of the electrocardiogram, *Q* the beginning of the QRS complex, and *T* the end of the T-wave in Lead I. The position of the opening snap (*X*) as calculated for *A* and *B* falls just at the point of angulation which apparently marks the end of the period of passive rotation. The gradual outward movement following this point must be due to ventricular filling. In *C*, a case of auricular fibrillation, the opening snap (*DS*) does not come at the point of angulation in the curve but follows it. Note that the slow outward movement of the ventricle does not begin until after the time of the snap. The position of the snap was calculated from measurements of its time relations to the T-wave of the electrocardiogram in beats with approximately the same preceding heart cycle length. In such beats the variation in the time interval between the end of the T-wave and the beginning of the snap does not tend to exceed 0.01 second.

parallax. By a comparison of these two records it was possible, if the rate remained fairly constant, to identify fairly accurately the point on the roentgen kymogram at which the opening snap occurred and thereby to relate it to a certain point in the excursion of the left ventricular border.

It will be seen in Fig. 10 that there is a point of angulation in the early diastolic part of the left ventricular curve. The sharp outward thrust

\*The roentgen kymograms were made by placing a horizontal slit 1.5 mm. wide over the part of the cardiac border whose movement was to be recorded. The film was moved past this point in a motor driven cassette holder at a constant rate and a continuous roentgen ray photographic record made. By this method the horizontal movement of the border may be recorded. Cardiac roentgen kymography was introduced by Gött and Rosenthal.<sup>18</sup> Simultaneous electrocardiograms and roentgen kymograms were published recently by Stenström and Westermarck,<sup>19</sup> but these authors reproduce only drawings of their results.

of the left ventricle which just precedes this point, begins too early to be caused by diastolic filling. It is due to rotation of the heart in the process of relaxation, after having been actively rotated in the opposite direction during systole. Following this point of sharp angulation the outward movement of the heart border is much more gradual. This gradual outward movement is due to ventricular filling. The position of the opening snap was approximately at this point of angulation in the roentgen kymograms in four of the six cases studied by this method (Fig. 10 A and B). In one case, however, the snap occurred before the movement of rotation was completed, and in another case it did not occur until an appreciable interval after rotation was completed and the ven-

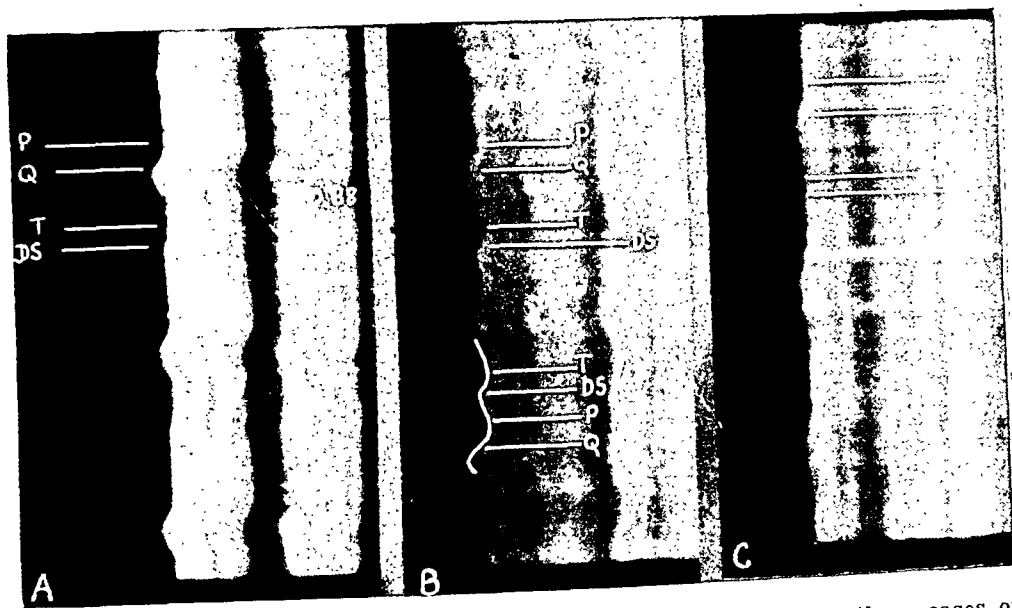


Fig. 11.—Roentgen kymograms of left auricular movement in three cases of mitral stenosis. The point *P* identifies the beginning of the P-wave of the electrocardiogram made simultaneously with the kymogram; *Q* identifies the beginning of the QRS complex, and *T* the end of the T-wave in Lead I. *DS* indicates the position of the opening snap (calculated from combined sound tracing and electrocardiogram). The chief excursion of the auricular wall in all three cases follows auricular contraction. In A and B, a distinct niche is observed at the instant of the opening snap. In C, the left auricle was very large and the excursion small. In this case, only a small niche appeared at the time of the snap.

tricular wall was practically motionless (Fig. 10 C). Thus while it may be said that the snap falls at about the time of the completion of passive rotation of the ventricles, it does not bear an exact time relationship to the process of rotation, since it may either precede or follow the end of rotation.

*Relation to Excursion of Left Auricular Border.* Roentgen kymograms of the left auricle were also attempted in a number of cases exhibiting a well-defined opening snap, and in normal controls. This procedure presents certain technical difficulties which need not be discussed here. The most satisfactory proof that the curve is due, at least in part, to auricular movement is the presence of a wave of contraction corresponding to the P-wave of the electrocardiogram. Satisfactory

curves have thus far been obtained in seven cases of mitral stenosis,\* in two normal controls and in two controls with mitral regurgitation.

It was thought that if the snap is due to sudden curtailment of the opening movement of the stenotic mitral valve, one should find in the movement of the left auricular wall a slight inward thrust just preceding the snap (due to the opening movement of the valve) and possibly also an outward thrust just after the snap (due to a reflected wave produced by sudden curtailment of valve movement). In five of the seven cases this prediction was fulfilled completely (Fig. 11). In the other two cases, however, no well-defined movement of the auricular wall in early

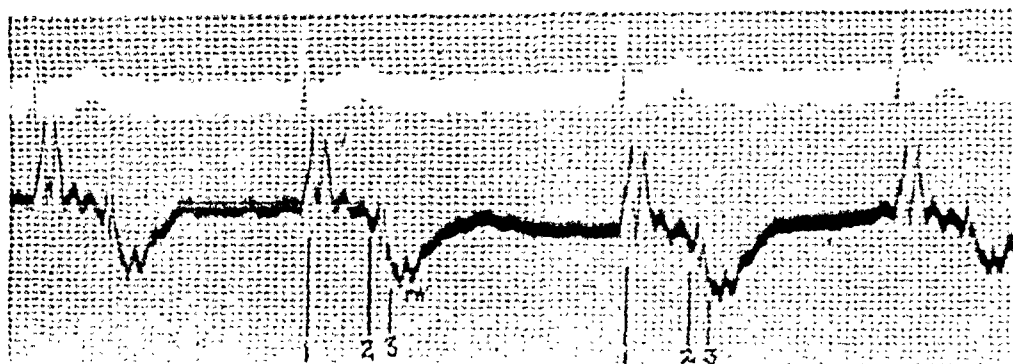


Fig. 12.—Mitral stenosis, opening snap, auricular fibrillation. Electrocardiogram and optically recorded apex cardiogram. The position of the snap on the apex cardiogram is calculated from similar cycles on a sound tracing recorded with the electrocardiogram. The snap precedes the beginning of the protodiastolic wave (PW) of the apex cardiogram, by approximately 0.04 second. This wave is usually insignificant when mitral stenosis is present.

diastole could be detected on the films. Possibly the failure in these two cases was due to marked dilatation of the left auricle and to high degree of stenosis, both of which would tend to minimize excursion of the auricular border. In none of the normal controls was the slight inwardly projecting niche seen.

*Relation to Apex Cardiograms.* Optically recorded apex cardiograms in mitral stenosis usually show either an insignificant protodiastolic wave or none at all. When apex cardiograms and the sounds are recorded without parallax, the opening snap usually precedes the beginning of the protodiastolic wave if one is present, by approximately 0.02 to 0.04 second (Fig. 12). This is in contrast to the relationship in protodiastolic gallop rhythm and the physiological third heart sound in which the peak of the wave and the gallop sound are practically synchronous (observations to be published).

#### MECHANISM OF PRODUCTION

The hypothesis that the opening snap is due to limitation of the opening movement of a stenosed mitral valve was supported by Guttman,<sup>3</sup> Sansom,<sup>4</sup> Rouches<sup>5</sup> and others substantially on the following evi-

\*This work is being carried further in the attempt to study the effect of mitral stenosis on the movements of the auricular wall.

dence: (1) The sound apparently occurs only in the presence of mitral stenosis. (2) It is heard best over the body of the heart or at the apex. (3) It is a short sharp sound such as might be expected from a valvular rather than a muscular event. (4) It apparently marks the beginning of the diastolic murmur. (5) It is not part of a reduplicated basal second sound.

Our observations indicate that the above statements require two modifications. The snap does not clearly mark the beginning of the diastolic murmur but tends to precede it by a short, although appreciable, interval. The point of maximum loudness of the snap is not at the apex, as was taught by both Guttman and Sansom and accepted since their time, but is slightly above and to the right of the position at which the murmur is best heard. These modifications do not weaken, but on the contrary rather strengthen the contention that the snap is produced by the opening of the stenosed mitral valve. Nevertheless such evidence can scarcely be regarded as conclusive, and it therefore seemed advisable to subject the hypothesis to further test for which the data described above were accumulated.

The following statements may be made regarding the mechanism of production of the sound:

1. Auricular beating is not concerned in the production of the snap. The sound is frequently present during auricular fibrillation. Moreover, when the auricles are beating coordinately, the snap occurs independently of auricular beats.

2. The snap is not due to reduplication of the second sound. It can be demonstrated by means of sound tracings that if the second sound becomes reduplicated, the snap tends to maintain its characteristic time relationship with one of the two components of the reduplicated sound. As has been pointed out above, there are certain circumstances under which the relationship is maintained with the first component and other circumstances under which it is maintained with the second component. Thus reduplication of the second sound and the opening snap should not be confused with each other.

3. Ventricular filling cannot be responsible for the production of the snap. In cases of fairly well-advanced mitral stenosis, the beginning of the murmur as registered in sound tracings tends to be marked by relatively large vibrations. The snap may precede these vibrations by as much as 0.04 second. Thus the snap comes before blood flow of significant amount from auricles to ventricles. Furthermore the nature of the valvular lesion tends to prevent precipitous ventricular filling. This is indicated by the fact that protodiastolic waves of the apex cardiogram are usually either insignificant or absent in mitral stenosis. These waves are practically synchronous with the beginning of the diastolic murmur. Moreover, if the snap were the result of ventricular filling, it should be

present in normal cases with mitral valves capable of opening widely, with no hindrance to ventricular filling.

4. Neither relaxation of the ventricles nor passive rotation to a resting position is responsible for the snap. The loudness and sharpness of the sound, as well as the position over which it is best heard, render such an explanation of its mechanism improbable. Furthermore, if this were the cause of the sound, it should be present in other hearts whose ventricles pulsate vigorously, such as are found in the presence of hyperthyroidism. The roentgen kymograms, however, show that, in some cases, the snap may occur either before or after passive rotation has been completed. This mechanism may, therefore, be excluded as a factor in the production of the sound.

5. The above-mentioned cardiodynamic factors having been excluded as responsible for the production of the snap, the problem apparently narrows itself to a consideration of the opening movement of the stenosed mitral valve. First of all, it is necessary to determine, as nearly as possible, whether this event occurs at the same instant as the snap. There are at least two methods by which evidence may be obtained on this point: (a) comparison of time relation of the snap to the descending limb of the jugular V-wave and (b) comparison with the movements of the left auricular border.

(a) According to Wiggers<sup>20</sup> the end of the isometric relaxation phase is marked by a drop in the venous pulse. This drop in venous pulse must be due to opening of the tricuspid valve permitting blood flow from the right auricle and veins into the right ventricle. If these events occur synchronously on the two sides of the heart, the beginning of the fall of venous pressure in the jugular phlebogram (descent of the V-wave) should mark the opening of the mitral valve as well as the tricuspid. Factors that influence one should have an equal effect on the other. If, therefore, the snap is due to sudden limitation of the opening movement of the mitral valve, it should occur at practically the same instant as the beginning of the descent of the V-wave, unless asynchronism of dynamic events in the two ventricular chambers is present.

The results of our studies in eight cases clearly demonstrate these time relations between the beginning of the descent of the V-wave and the snap. It is equally significant that these two events are practically simultaneous when the second sound is single (and dynamic phenomena on the two sides of the heart practically synchronous) and that they are not simultaneous when the second sound is split. These facts indicate that the snap is related to opening of the mitral (but not the tricuspid) valve.

(b) The results obtained by left auricular roentgen kymography have a bearing on the mechanism of the snap. The presence in five out of seven cases of a distinct inward thrust in the curve of left auricular

movement, which ends at the instant the snap occurs and is followed by a short outward movement indicates that the process of auricular emptying is temporarily interrupted at the very beginning of the process. In the two cases that this phenomenon could not be recognized the left auricles were very large, so that little movement of the wall occurred at any time. In the two normal cases and also in the two cases of mitral regurgitation without stenosis, in all of which the excursions of the left auricle were fairly wide, this peculiar niche in the curve was absent. It is clear from these data that the snap occurs as the auricle makes its first attempt to empty and that in cases in which the snap is present, there tends to be a temporary interruption of the emptying process immediately after the snap. The outward movement of the auricular wall following the inward movement could be caused by (1) a reflected wave from the mitral valve whose opening movement was suddenly curtailed; (2) inflow of blood from the pulmonary veins, auricular emptying having been temporarily retarded; or (3) a combination of these two factors. In any event the snap is identified in time with the sudden curtailment in the opening movement of the mitral valve.

Thus all the evidence we have been able to collect is consistent with the hypothesis that the snap is due to sudden curtailment of the opening movement of the mitral valve.

At this point the hypothesis proposed by Gallavardin,<sup>9</sup> that the sound is due to a "shock-like" wave transmitted from the aortic to the mitral valve must be considered, particularly since it has been supported recently by Mozer and Duchosal.<sup>13</sup> Two objections to this hypothesis should suffice: (1) Even if it were conceivable that a wave could travel so slowly from the aortic to the mitral valve as to produce a sound after 0.06 to 0.15 second, it would not be possible for such a slowly advancing wave to be responsible for the production of a sharp sound. (2) The fact that the summit of the V-wave and the snap occur simultaneously (when the second sound is single) even in cases of arrhythmia in which the time intervals after the second sound may vary considerably from beat to beat, eliminates Gallavardin's hypothesis. The hypothetical "shock-like" wave could not be expected to vary its speed from the aortic to the mitral valve in correspondence with variation in the interval between the second sound and the summit of the V-wave, since the time of the latter is determined by the beginning of right ventricular filling, whereas the former would have to depend on aortic closure.

In justice to Gallavardin, it should be stated that at the time his hypothesis was proposed, he assumed that the mitral valve opened immediately after aortic closure. The development of physiological knowledge regarding the time intervals between semilunar valve closure and A-V valve opening (the so-called isometric relaxation phase) has made his hypothesis untenable.

The evidence in favor of the view that the snap is produced by sudden limitation of the opening movement of the stenosed mitral valve may be summarized as follows: (1) The sound apparently occurs only in the presence of mitral stenosis. (2) It is the type of sound which might be expected from sudden vibration of a valve. (3) The position at which it is best heard favors its production either at the mitral valve or in its vicinity. (4) It is entirely independent of auricular contraction. (5) It precedes both the diastolic murmur and effective ventricular filling. (6) It may be synchronous with, precede or follow the completion of passive rotation of the ventricles. (7) It comes, as is shown by combined sound tracings and jugular phlebograms and by auricular roentgen kymograms, at the instant when opening of the mitral valve is to be expected. (8) So far as is known, no other cardiac event capable of producing a sound is occurring at this instant.

#### DIFFERENTIAL DIAGNOSIS

The chief reason why the opening snap has failed to win for itself prominence as a diagnostic sign of mitral stenosis is due to the fact that it has never been clearly enough differentiated from certain other sounds. The confusion which exists is exemplified in a recent contribution by a distinguished investigator of rheumatic heart disease,<sup>21</sup> who writes that one of the signs of mitral stenosis is a doubling of the second sound at the apex. The writer apparently appreciates the diagnostic significance of this physical sign. The term is unfortunate, since, as has been pointed out above, (1) doubling of the second sound is not characteristic of mitral stenosis and (2) neither doubling of the second sound nor the opening snap is heard best at the apex.

The sounds which must be considered in the differential diagnosis of the opening snap are: (a) reduplication of the second sound; (b) protodiastolic gallop sounds; (c) the physiological third heart sound; and (d) midsystolic clicking sounds. The important differential points include: (1) character of the sounds; (2) areas over which they are best heard; and (3) time relations.\*

The character of the sounds and the area of maximum audibility are best determined by auscultation and the time relations by sound registration. It is possible, however, to train the ear to detect remarkably small differences in short intervals. In our experience the trained observer learns to estimate from auscultation the duration of intervals up to 0.12 second with an accuracy of approximately  $\pm 0.02$  second.

(a) Reduplicated second sounds are heard best either at the level of the second or third, rarely the fourth interspace, over the sternum or just to the left of it. The sounds are always louder at the base than in

\*We have recently constructed a table in which certain important characteristics of the various "extra" heart sounds of value in the differential diagnosis are given.<sup>22</sup>



the area over which the opening snap is heard best. Localization is usually more readily made in the case of high-pitched, sharp sounds whose character resembles that of the snap. The time interval between the two sounds is usually shorter than in the case of the snap but occasionally does exceed 0.06 second. Under such circumstances, the time relation loses its value as a differential point. There is frequently marked phasic respiratory variation in the intervals between split second sounds. Phasic variation between the second sound and the snap in the absence of arrhythmia is so slight as to be inappreciable on clinical examination.

(b) The protodiastolic gallop and (c) physiological third heart sounds are so similar in their characteristics that they may be considered together in the differentiation from the snap. They are heard best, as a rule, in the neighborhood of the apex.\* They are low-pitched, dull sounds, thus differing strikingly in character from the opening snap. These sounds occur in a range of approximately 0.12 to 0.20 second after the second sound, the length of the interval depending to some extent on the cardiac rate.† If the influence of cardiac rate on the interval is taken into consideration, there are comparatively few cases in which this time relation loses its value as a differential point.

(d) Clicking or snapping sounds sometimes occur during ventricular systole,<sup>22</sup> coming between the first and second sounds. These sounds frequently resemble the opening snap and sometimes have a similar area of maximum audibility. They will not be confused, however, if the examiner orients himself as to which is the first and which the second sound.

#### CLINICAL IMPORTANCE OF THE OPENING SNAP

The opening snap may be regarded as having a value for the diagnosis of mitral stenosis scarcely second to that of the characteristic diastolic murmur. In this respect it has two great advantages: (1) It is easily differentiated from all other sounds, and (2) it is clearly audible in many cases in which the murmur is so insignificant as to be easily missed. It may, therefore, save the examiner the embarrassment of failing to hear a significant murmur. Furthermore, it is present in some cases in which the murmur cannot be elicited. In every case of this type which we have observed, there were other signs pointing to the diagnosis of mitral stenosis.

According to Rouches, the sound is absent either in very early or in advanced mitral stenosis, in the former because the valves are not bound down enough to snap and in the latter because they have lost their mobility. We have not been able to make sufficient necropsy examina-

\*There is one exception to this statement. Right-sided gallop rhythm is usually heard best in the neighborhood of the lower part of the sternum.

†Unpublished observation.

tions of material studied clinically to confirm or to disprove Rouches' view. In five cases, however, in which we failed to elicit the opening snap, the valves were found to be greatly thickened and practically immobile. Another point which might be regarded as in favor of Rouches' hypothesis is the fact that the snap is less frequently heard in young children with mitral stenosis, than in adults. Whether this is because valve crippling is usually less advanced in children is not known.

The evidence, therefore, appears to indicate that the presence of the opening snap may be regarded as practically pathognomonic of mitral stenosis. Its absence, however, is not to be construed as a point against the diagnosis.

#### SUMMARY

1. The opening snap (*claquement d'ouverture de la mitrale*) can be heard and recorded in more than half the cases of mitral stenosis. It has not been observed in the absence of mitral stenosis. It is one of the most important diagnostic signs of this valvular lesion.

2. The chief characteristics of the opening snap are the following: (a) The sound is a sharp snap or click. (b) It has been found to occur from 0.03 to 0.19 second after the beginning of the second sound, the ordinary range being 0.06 to 0.11 second. (c) It is usually loudest in the fourth left interspace, occasionally in the third, slightly above and to the right of the area in which the diastolic murmur is best heard. (d) It precedes the onset of the murmur by a short interval. (e) It is usually best elicited with the patient in the recumbent position. (f) In some cases it can be brought out by exercise and by increase of the cardiac rate. (g) It tends to be louder when the rate is rapid.

3. The interval between the second heart sound and the opening snap is influenced by the cardiac rate, tending to become shorter as the rate increases. Variations in the duration of this interval occur during auricular fibrillation and sinus arrhythmia depending on the length of the preceding heart cycle.

4. The opening snap is easily differentiated from reduplication of the second sound, protodiastolic gallop sounds, the physiological third heart sound and systolic clicking sounds.

5. The time relations of the opening snap, as observed from comparisons of sound tracings with electrocardiograms, apex cardiograms, jugular phlebograms, auricular and ventricular roentgen kymograms, exclude auricular contraction, ventricular rotation or filling, or shock-like waves transmitted from the aortic to the mitral valve, as factors in its production. All the evidence thus far available is in accord with the hypothesis that the sound is produced by the sudden limitation of the opening movement of a stenosed mitral valve which occurs in early diastole as soon as the left ventricle relaxes sufficiently to permit the pressure of the auricular blood column to become effective.

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# THE FORM OF PREMATURE BEATS RESULTING FROM DIRECT STIMULATION OF THE HUMAN VENTRICLES\*

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IN 1930, Barker, Macleod and Alexander<sup>1</sup> reported the first observations upon the form of electrocardiographic curves derived from artificial stimulation of known areas upon the exposed human ventricles. A large number of points upon the epicardial surface of both ventricles were stimulated electrically, and the resulting deflections were recorded simultaneously in the three customary leads of the electrocardiogram. The curves were such as to lead these authors to conclude:

“(a) Ventricular premature contractions of right ventricular origin are represented in the electrocardiogram by ventricular complexes in which the chief initial deflection is upward in Lead I. Ventricular premature contractions of left ventricular origin are represented in the electrocardiogram by ventricular complexes in which the chief initial deflection is downward in Lead I.

“(b) The clinical electrocardiograms at present ascribed to block in the right branch of the His bundle indicate block in the left branch, and vice versa.

“(c) In so-called left ventricular preponderance the electrocardiogram is dominated by right ventricular effects and vice versa.”

The conclusions drawn from their observations are of such importance to physiology, and the subsequent work to which they have led is so far-reaching in its implications that it has seemed desirable they should not rest upon a single case. Clearly, the opportunities for similar observations do not often present themselves, but we have recently been able to repeat the crucial part of their observation by inducing premature beats under direct observation from the two ventricles. It has seemed of some importance to place these upon record as confirmation of the valuable contribution of Barker and his collaborators, because observations upon a single patient, however precise and extensive they may be, are always subject to the criticism that the patient might have been exceptional in some important respect.

The patient, a man of thirty-eight years, entered the hospital on May 27. He had suddenly developed, eight days previously, pain in the left side of the anterior chest, fever, cough and sputum. He became steadily worse, and was gravely ill at the time of his admission to the hospital. The temperature was 103°, the pulse rate 130 and the respirations 30 per minute. Physical examination revealed clear signs of fluid in the right pleural cavity, with considerable displacement of the heart

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to the left. There was also a widespread pericardial friction rub. A needle was inserted into the pleural cavity through the fourth right intercostal space anteriorly, and a considerable quantity of greenish-yellow pus withdrawn. A direct smear from this material showed lancet-shaped diplococci, and cultures yielded Type 3 pneumococci.

The patient was immediately transferred to the Surgical Service and thoracostomy was performed, a portion of two ribs being removed in the right anterior axillary line, and suction drainage started. Despite fairly satisfactory drainage of the empyema cavity, the patient's general condition did not improve. On June 6, exploratory puncture of the peri-

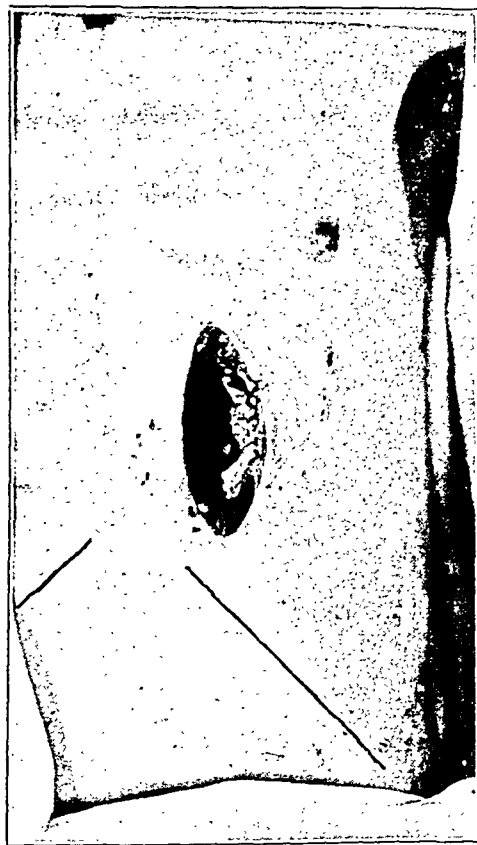


Fig. 1.—Photograph of thorax showing location of the opening through which the ventricles were stimulated. The approximate line of the costal margin is indicated by ink lines.

cardium revealed pus, and pericardiotomy was performed at once, with the removal of about 600 c.c. For the next few days he seemed slightly better, although the purulent discharge from the pericardium did not decrease, but after June 15 he grew steadily worse and died on June 19.

It is of some importance to state that this man had been in the hospital two years previously because of acute lobar pneumonia. Physical examination and roentgenograms at that time revealed no evidence of heart disease. He had never suffered from dyspnea on ordinary exertion, from orthopnea, or edema of the lower extremities, and stated that he

had never had rheumatic fever, chorea, tonsillitis, scarlet fever or diphtheria. It seems highly probable, therefore, that his heart was normal at the beginning of the acute illness from which he died. Careful postmortem examination of the heart failed to disclose evidence of disease of the myocardium or valves.

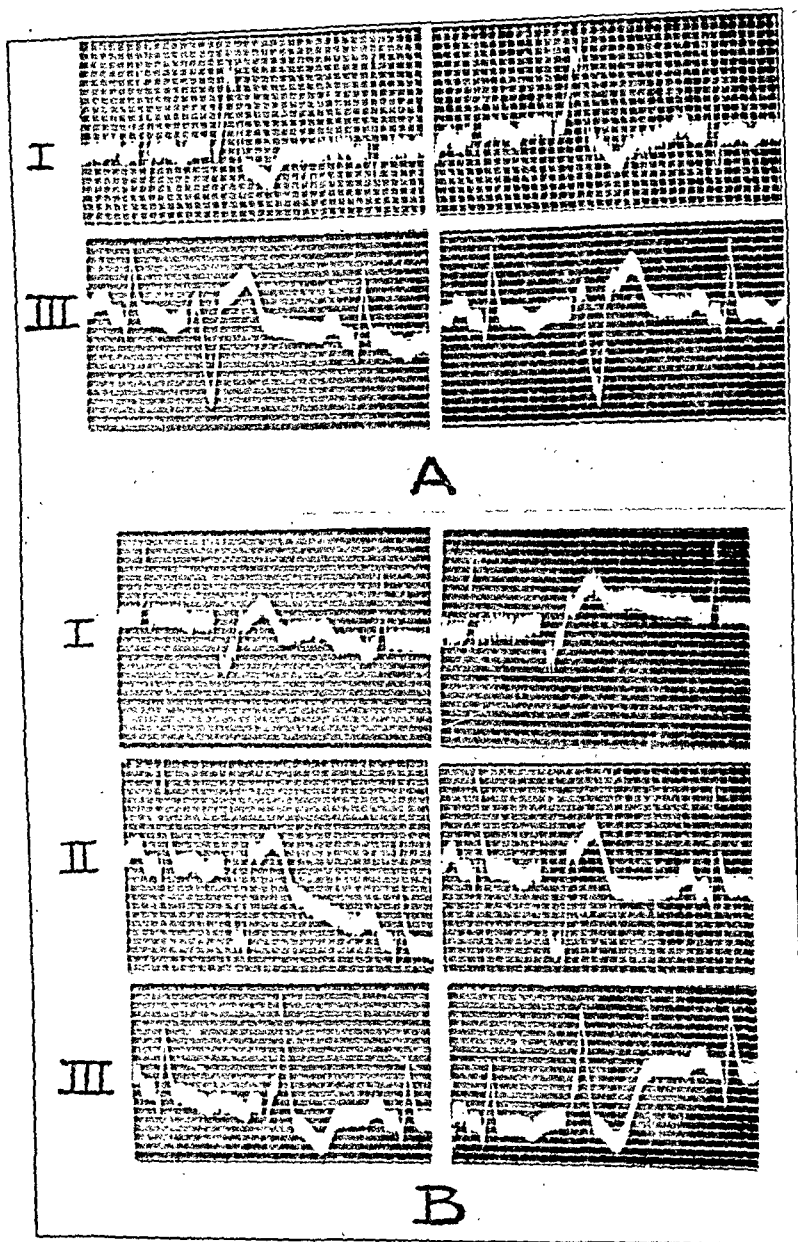


Fig. 2.—A. Leads I and III recorded during stimulation of the right ventricle. The curves on the right were secured two days after those on the left, and are precisely similar. B. The usual three leads recorded consecutively during stimulation of the left ventricle. The curves on the right were registered about fifteen minutes after those on the left. In Lead I the downward deflection of the premature beat measures 1.1 millivolt, but is largely lost in reproduction.

On June 13, the patient seemed sufficiently well to permit brief observations, and with his consent these were made. The pericardium was irrigated until the returning fluid was almost entirely clear, and the sac drained as thoroughly as possible by means of suction. The wound as

shown in Fig. 1 diminished in size as it penetrated the chest wall; it was actually funnel-shaped, so that the area of the heart's surface exposed to direct view was not large. It was very easy to stimulate the same point time after time without using landmarks other than the lower margin of the wound. A portable electrocardiograph was placed at the side of the patient's bed, and the usual attachments were made to the arms and left leg. Numerous attempts were then made to elicit premature beats by mechanical stimulation of the surface of the ventricle (tapping, pinching, etc.) but these were fruitless. We then connected an ordinary type of stimulating electrode to the secondary cell of an inductorium, so arranged as to deliver single break shocks upon opening a switch, and placed the points (separated by an interval of approximately 2 mm.) upon the surface of the heart. The strength of the current was not



Fig. 3.—Post-mortem photograph of the heart in situ, with the pericardium reflected. The white disc on the anterior surface lies upon the area actually stimulated; the arrow points to the level at which the posterior electrode was applied, but the actual point of stimulation is not shown.

actually measured; it was sufficient to produce a muscle-twitch when applied to a motor point on the normal moist skin.

One of us kept the electrodes applied to the heart and signalled to the nurse when stimuli were desired; the other watched the movements of the string shadow upon the face of the camera and photographed the beats when it was clear that the contact was satisfactory. The leads were recorded in sequence, not simultaneously. Numerous records were secured, of which only two are reproduced in Fig. 2A. It should be emphasized that the electrodes were removed and reapplied many times; the ectopic beats were precisely similar in all records.

Two days later it was possible to repeat these procedures; in addition, we had prepared electrodes to pass around the curve of the heart's left

border and stimulate the posterior surface. In appearance, these were not unlike the figure 5 without its top bar, or the lower half of the letter S. The extreme tip only was exposed, the remainder of the wire being covered in such a way as to permit its sterilization. With considerable difficulty this electrode was inserted through the wound and rotated in such a way as to bring its point against the posterior aspect of the heart a short distance above the apex. In this attempt, as in the earlier one, it was possible to be sure of the point of stimulation with considerable exactness, since adhesions had formed between the lower part of the pericardium and the heart, and the electrode was simply placed as far toward the apex as possible. The electrodes were withdrawn and re-inserted four times, and the ectopic beats resulting from each procedure were identical. They are shown in Fig. 2B.

After death, the two areas used for stimulation were identified and marked through the same wound before the chest was opened. The anterior wall of the thorax was then removed; markers were placed to indicate the points of stimulation, and a photograph was taken (Fig. 3). The white disc marks accurately the spot upon the right ventricular surface that was used; the white arrow points merely to the approximate location of the stimulus on the left ventricle, as the electrode points were actually behind the heart. Long needles were then inserted deeply through these two spots, at right angles to the surface, and the heart was opened. The anterior needle was found to have entered the right ventricular cavity approximately 2 cm. from the interventricular septum and 3 cm. from the apex; the posterior one had entered the left ventricular cavity approximately 1.5 cm. from the septum and 4 cm. from the apex. These points apparently do not correspond accurately with any of those used by Barker and his coworkers; the one on the right ventricle lies between their points 6 and 9, while that on the left ventricle is apparently a little nearer the base than their point 12, but not so high as their point 11; it lies between their 3 and 12 and slightly higher than either. However, it would be obviously almost impossible to use points in exactly corresponding locations in two consecutive human hearts, and it is quite sufficient for the purpose of this report to know that the stimulated points lay on the lower portions of the right and left ventricle respectively. The curves derived from stimulation of these areas are to be compared with those shown in Figs. 7A, 7B, and 8 of their paper.

It is clear that the premature contractions induced by stimulation of the right ventricle in our patient are similar in all important respects with those registered by Barker, Macleod and Alexander from stimulation of the corresponding area in their patient (their points 6 and 8). In both cases, the curves are discordant, the chief initial deflections being upward in Lead I and downward in Lead III, and the terminal deflections are opposite in direction to the initial ones.



The deflections resulting from stimulation of the left ventricle in our patient, however, differ from those obtained from the earlier case in one respect; we consistently obtained discordant curves, the exact reverse of those from the right ventricle; that is, the chief initial deflections were downward in Lead I and upward in Lead III. In the first reported case, however, (1) concordant curves were obtained from all points on the apical portion of the left ventricle, and curves similar to ours from only one point (their point 1) higher toward the base. There are several possible explanations for this difference, but it is unnecessary to pursue the inquiry, since the important deductions seem clear.

Stimulation of the right ventricle in our patient, as in theirs, yielded discordant curves of which the chief initial deflections were upward in Lead I; stimulation of the left ventricle in both cases yielded complexes of which the chief initial deflections were downward in Lead I. The precise and extensive observations of Barker and his collaborators are confirmed in their most important respect by these very limited observations, and the conclusions drawn from their curves are strengthened by the ones here published.

#### SUMMARY

Premature contractions evoked by electrical stimulation of one spot upon the right ventricle and one upon the left ventricle of a partially exposed human heart have been recorded in the three standard leads of the electrocardiogram. These were not taken simultaneously, but consecutively.

We are able to confirm the observations of Barker, Macleod and Alexander, who first showed that premature contractions derived from stimulation of the right ventricle have the chief initial deflection upward in Lead I, while those from stimulation of the left ventricle have the chief initial deflection downward in Lead I.

These records are published merely as confirmation of their work, which has hitherto rested upon curves obtained from a single case.

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## ELECTROCARDIOGRAPHIC CHANGES FOLLOWING LIGATION OF THE CORONARY ARTERIES OF THE DOG\*

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EVER since the perfection of the electrocardiogram and its employment in the study of cardiac disease, clinicians have had a keen interest in establishing correlations between abnormal electrocardiograms and types and degree of cardiac injury. Although knowledge of the mechanism of production of the T-wave has been incomplete, yet the clinical importance of significant inversions of the T-wave in prognosis was conclusively established by Willius. One of us<sup>1</sup> undertook, in 1926, a careful anatomicopathological study of the hearts of 120 subjects who had come to necropsy, and who had exhibited significant inversions of the T-wave in life. It was hoped that certain inversions of the T-wave might be correlated with lesions demonstrable by anatomical or pathological means and possibly with certain types or situations of these lesions. This investigation, although in the main disappointing, indicated that with the exception of myocardial infarction, significant T-waves were not to be explained by lesions in the myocardium as demonstrated by ordinary pathological methods.

In addition, this investigation, coupled with clinical observations, led to the hypothesis that T-wave negativity could result from injury to the myocardium, the result of strain predominantly of either the right or the left ventricle. Furthermore, it seemed evident that such strain need not be manifested in the myocardium, except as hypertrophy, and at times as dilatation of one or the other ventricles. These conclusions were substantiated by the investigations of Barnes and Whitten.<sup>2, 5</sup> In addition, it was established that inversions of the T-wave were specific for the ventricle that was subjected to excessive strain; strain predominantly of the left ventricle was associated with inversion of the T-waves in Lead I or Leads I and II; strain predominantly of the right ventricle, with inverted T-waves in the combined Leads II and III. It was pointed out that these conclusions were in harmony with the experimental observations of Daly and Otto.

Barnes and Whitten<sup>3, 6</sup> also found that coronary occlusion and acute myocardial infarction produced characteristic modifications of the R-T and S-T components of the electrocardiogram, by which one could predict whether the infarction involved the posterior basal portion of the left ventricle and the adjacent interventricular septum, on the one hand, or the anterior portion of the left ventricle and apex on the other. This localization was possible because infarction in the poste-

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rior basal portion of the left ventricle produces electrocardiographic changes which are the exact reverse of those produced when the infarction involves the anterior and apical portions of the left ventricle.

These observations clearly suggest, if one may judge from the changes observed in the RS-T component of the electrocardiogram, that the heart of man is oriented to the conventional leads of the electrocardiogram in such a way that the electrical forces existent when acute infarction involves the posterior basal portion of the left ventricle are opposed to those present when acute infarction of its anterior and apical portion occurs. They indicate, further, that the right ventricle as a whole produces electrical forces which act on the T-wave in a manner opposite to those produced in the left ventricle, at least in its apical and anterior portion. The conception can be entertained that the opposition of electrical forces produced in the right and basal portions on the one hand, and in the apical and left portions on the other hand, in the heart of man determines the form of the RS-T segment and the direction of the T-waves. This conception is supported by experiments on the dog's heart, showing that injury to one ventricle produces effects on the electrocardiogram opposite to those produced by injury to the other ventricle. In axial leads it has been shown that a negative effect on the T-wave is produced by cooling the left ventricle,<sup>8, 13, 20, 24</sup> freezing the right ventricle,<sup>13</sup> ligation of the right coronary artery,<sup>14</sup> acute right ventricular strain,<sup>7</sup> stimulation of the right accelerator nerve,<sup>15</sup> and injection of alcohol (95 per cent) into the right ventricle.<sup>10</sup> A positive effect on the T-wave was produced by cooling the right ventricle,<sup>8, 13, 20, 24</sup> freezing the left ventricle,<sup>13</sup> ligation of the circumflex branch of the left coronary artery,<sup>14</sup> acute left ventricular strain,<sup>7, 12</sup> stimulation of the left accelerator nerve,<sup>15</sup> and injection of mercuric chloride or silver nitrate into the right ventricle.<sup>8</sup> A high take-off of the R-T component of the electrocardiogram was observed following injection of mercuric chloride,<sup>8</sup> silver nitrate<sup>8</sup> or alcohol (95 per cent)<sup>10</sup> into the left ventricle, whereas a low origin of the S-T component from the S-wave occurred when these substances were injected into the right ventricle.

Smith's<sup>18, 19</sup> investigations led him to conclude that in the dog the modifications of the electrocardiogram characteristic of infarction were produced experimentally only by ligation of the branches of the left coronary artery. Parkinson and Bedford,<sup>17</sup> in a consideration of their electrocardiographic studies of coronary occlusion, concluded that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches which produces characteristic T-wave changes." Katz,<sup>10</sup> in his review of the literature, reached the conclusion that inverted T-waves "occur in coronary involvement only when the left coronary artery is affected either clinically or experimentally." Barnes and Whitten's<sup>6</sup> work established conclusively the

fact that infarction produced by occlusion of the right coronary of the human being produced as characteristic a change in the RS-T wave as did occlusion of the left coronary artery. Otto,<sup>14</sup> using an axial lead, found that ligation of the circumflex branch of the left coronary artery of the dog (distributed exclusively to the left ventricle) increased the positivity of the T-wave; ligation of the right coronary artery (supplying the right ventricle) caused increased negativity of the T-wave, whereas ligation of the anterior descending branch of the left coronary artery (about equally distributed to the right and left ventricles) produced effects partially characteristic of each of the first two types of ligation.

#### PURPOSE AND METHOD OF STUDY

The present study represents a further investigation of the effects of ligation of the branches of the coronary arteries of the dog that go, respectively, to the right and to the left ventricle on the RS-T component of the electrocardiogram, using the standard electrocardiographic leads. Its chief object was to determine the difference between the electrocardiographic tracing before and after ligation of the right and left coronary vessels, and to see to what extent such changes as occurred could be compared with the change known to occur in the electrocardiogram exhibited by man following infarction. It seemed important to use all three conventional electrocardiographic leads, inasmuch as it is impossible to predict the changes in the T-wave which will occur in Leads I and III from a study of the changes of the T-wave observed in axial leads. Certainly by using the three conventional leads, one is better able to compare the changes obtained with those observed in the electrocardiogram of man.

The following method was employed in these experiments: Dogs were anesthetized with ether; the thorax was surgically prepared, and a tracheal cannula was introduced for maintenance of positive pressure. The left intercostal spaces were exposed, and the thorax was opened through the fourth left intercostal space. The adjacent ribs were forcibly separated by a retractor, permitting good exposure of the heart. The pericardium was incised, and, if desired, the coronary vessels were ligated. No attempt was made to exclude the vena comites from the ligation. The heart was allowed to fall back into the pericardial sac, but the pericardium was not closed by suture. The thorax was then closed.

Electrocardiograms were taken before an anesthetic was given, and in most instances both before and immediately after operation while the dog was anesthetized. No attempt was made to determine the blood pressure at the time the electrocardiograms were made. Electrocardiograms made immediately after operation actually were taken about twenty minutes after the coronary branches were ligated. This time was consumed in closing the thorax and carrying the animal to a separate room to make the electrocardiogram. Electrocardiograms were then made on the afternoon following operation, on the first and second days after operation, several times in the first two weeks, and after that at irregular intervals, until the dog died or was killed. Necropsy was performed after death in all instances which have been included in arriving at conclusions.

Before describing the results it is important to comment on certain features of the electrocardiograms of dogs. First of all, so far as the T-waves are concerned, they differ from those encountered in work with human beings. The most striking difference is the extreme variability of the T-waves in the normal electrocardiogram of the dog. The T-waves may be negative in Lead I, in Leads I and II, or even in Leads I, II and III in the normal dog. Furthermore, it appears that the same procedure may produce in the T-waves of a dog of which the T-wave was normally positive in Lead I, changes that are different from those obtained when the T-wave was originally negative in Lead I. So it appears that to compare the results of similar experiments it is essential to know the nature of the T-waves before the experiment is begun. Serial tracings following operation are essential if one is to compare the results with those obtained in studies of man following coronary occlusion. It is necessary to understand wherein the coronary circulation of the dog differs from that of man.<sup>11, 21</sup>

The literature dealing with the electrocardiographic effects of experimental obstruction of the coronary arteries of the dog is often lacking in data relating to control experiments. In our control experiments, which will be considered first, we duplicated every step of the ordinary experiment except that the coronary arteries were not molested. In one control experiment, the pericardium was vigorously manipulated.

*Control experiment 1.*—The electrocardiogram before anesthesia contained a sharp, positive T-wave in Lead I (Fig. 1, dog 1). The pericardium was opened in the usual manner, the heart was lifted out of the pericardial sac, but ligatures were not placed about the coronary arteries. The afternoon following operation, a deep, abrupt, negative T-wave was present in Lead I;  $T_2$  was now sharply negative, and  $T_3$  was exaggerated and positive. On the fourth day, positive T-waves appeared in Leads I and II, continued to increase in height with elevation of the R-T segment until the twenty-fifth day, and then disappeared. Then the T-waves in Leads I and II became inverted and remained so until the eightieth day, after which the dog was killed.

In study of dog 2, subjected to a similar operative procedure, and in which the T-wave of the electrocardiogram was sharply positive in Lead I, similar negativity of the T-waves in Leads I and II appeared, and  $T_3$  became sharply positive in Lead III immediately after operation and remained so until the death of the dog one day after operation. In the electrocardiogram, taken under ether following operation, no significant change in the level of take-off of the T-wave from the R- or S-wave occurred, but the R-T segment in Lead II showed a distinct, negative troughlike effect.

In a like experiment on dog 3 (Fig. 2) of which the tracing taken before the anesthetic was given contained a positive T-wave of very low voltage in Lead I, negativity of the T-waves following opening of the pericardium and manipulation of the heart did not occur, but there did appear increasing positivity of the T-waves in Leads I and II, which became greatly exaggerated on the ninth day after operation. In the tracings of this dog, taken immediately after operation under ether, changes were not observed in the levels of the RS-T segment. The T-waves in the tracing taken forty-two days after operation assumed the same direction as those in the original preoperative tracings.

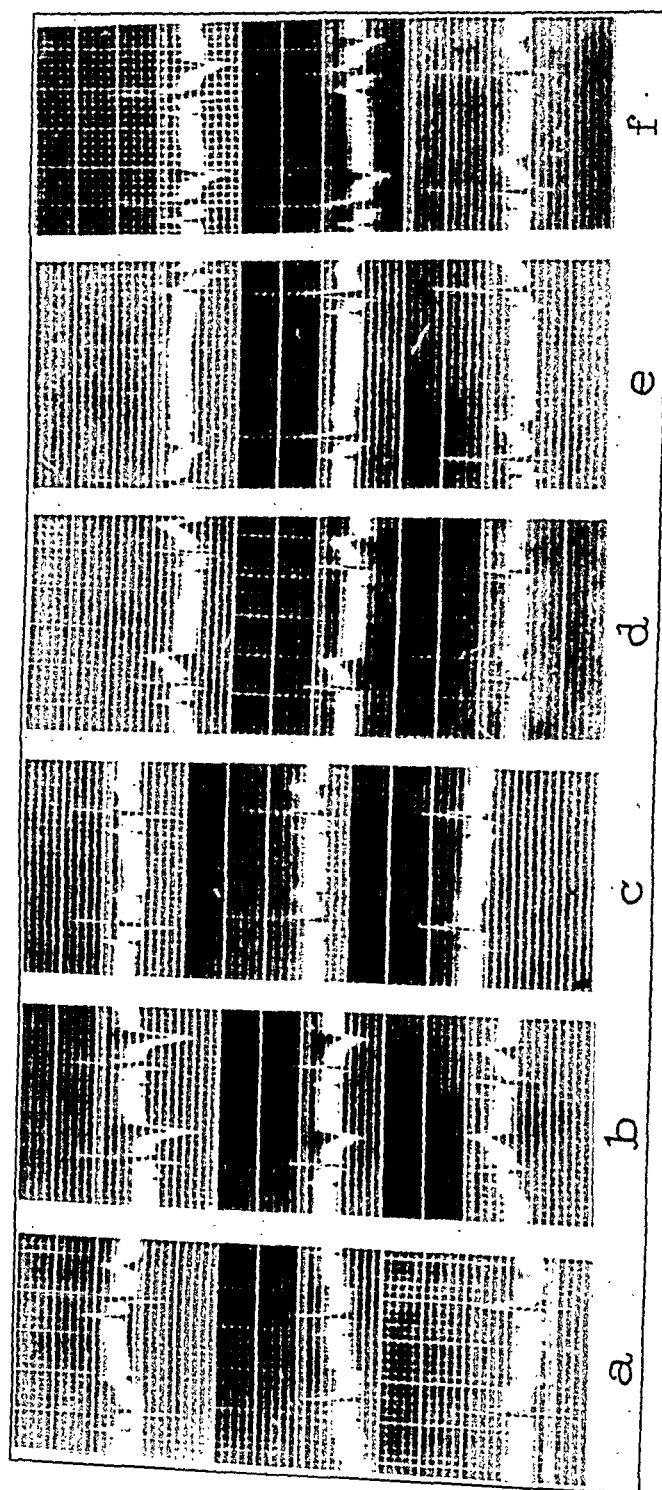


Fig. 1.—Dog 1. The pericardial sac was opened but the coronary arteries were not ligated. The electrocardiograms included here were taken: *a*, five days before operation; *b*, in the afternoon following operation; *c*, four days after operation; *d*, nine days after operation; *e*, fifty-four days after operation; *f*, seventy-two days after operation.

*Necropsy.*—Dog 1 was killed five and one-fourth months after operation. The pericardium was adherent over the basal three-fourths of the heart. There were no pericardial adhesions about the apex and anterior half of the left ventricle. The myocardium, the endocardium and the valves were normal.

Dog 2 died one day after operation. The pericardium had been incised. The coronary vessels were normal and not obstructed. There was no evidence of myo-

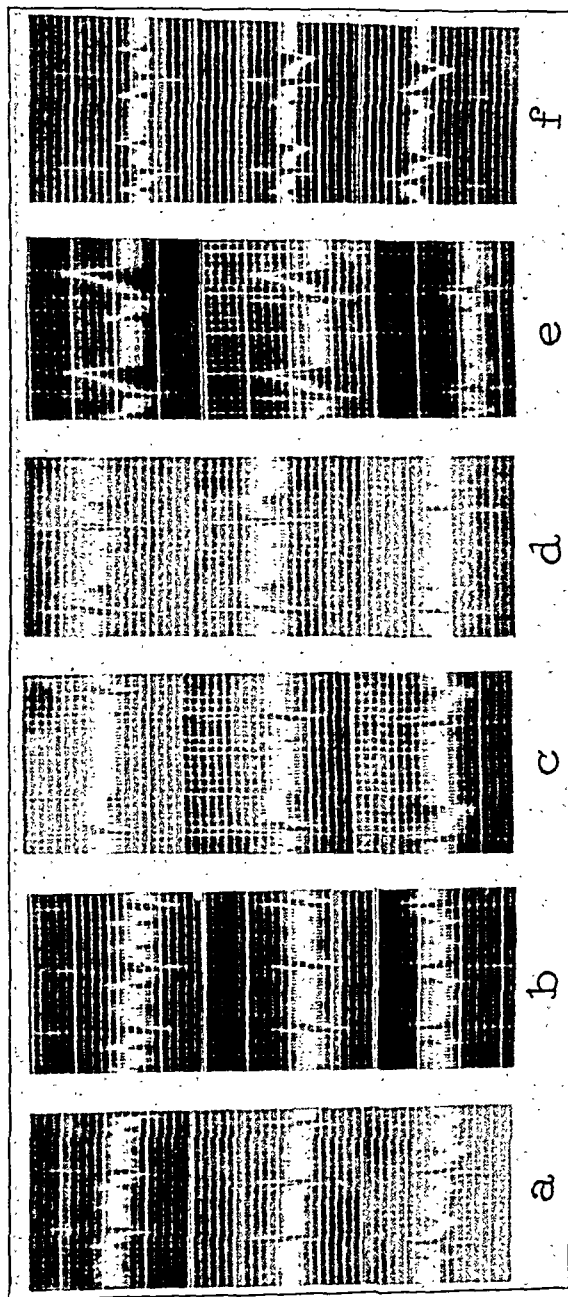


Fig. 2.—Dog 3. The pericardial sac was opened, but the coronary vessels were not ligated. The electrocardiograms were taken as follows: *a*, five days before operation; *b*, immediately before operation under ether anesthesia; *c*, afternoon after operation; *d*, five days after operation; *e*, nine days after operation; *f*, forty-two days after operation.

cardial infarction and there was no cardiac hypertrophy. The valves and endocardium were normal.

The pericardial sac of dog 3 had been opened, but the coronary vessels had not been ligated. The pericardium was adherent over the basal three-fourths of the heart. The apex and anterior half of the left ventricle were free of pericardial adhesions. There was no evidence of myocardial infarction. The valves and endocardium were normal.

*Control experiment 2.*—In the electrocardiograms of dog 4, the T-wave was negative in Lead I and positive in Lead III in the tracing taken before operation. Here, in one instance, in which the pericardium was opened but the coronary arteries were not molested, the T-wave became positive in Leads I and II; in Leads II and III the T-waves became exaggerated on the tenth day (Fig. 3, dog 4). The electrocardiogram returned essentially to normal on the forty-third day and remained so until the dog was killed. The electrocardiogram of dog 5, taken before operation showed T-waves similar to those observed in the electrocardiogram of the fourth dog. In the electrocardiograms of dog 5 taken after the same type of experimental procedure as carried out on dog 4 the increased positivity of the T-waves in Leads II and III appeared, but the T-wave in Lead I never became positive. The tracing returned

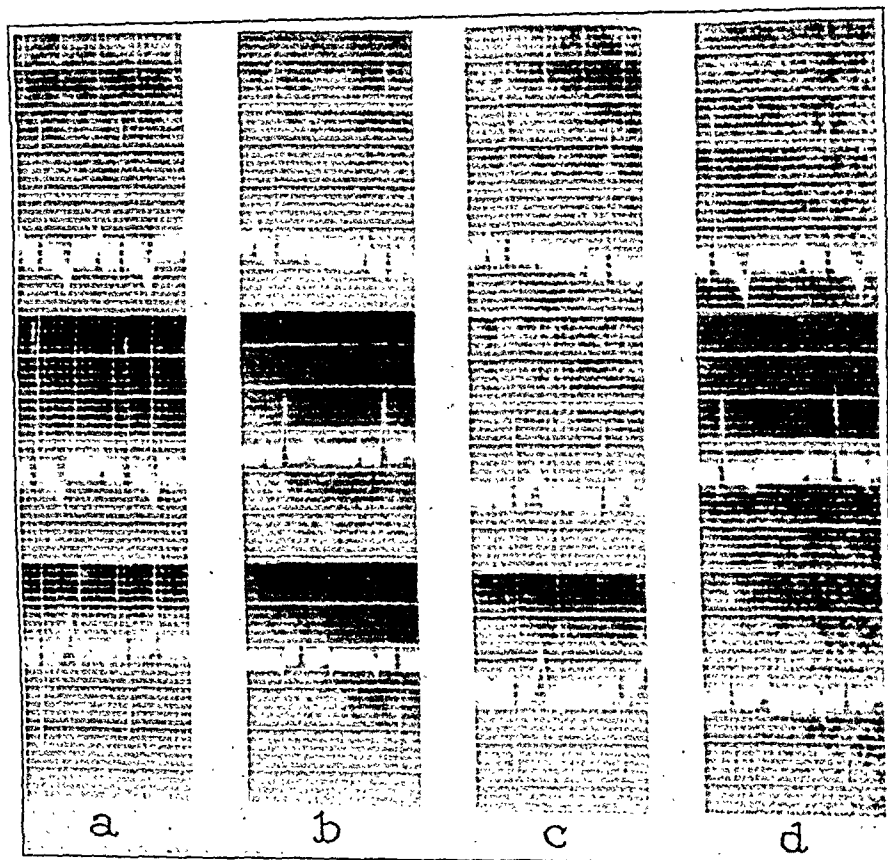


Fig. 3.—Dog 4. The pericardium was opened, but the coronary arteries were not ligated. The electrocardiograms were taken as follows: a, four days before operation; b, four days after operation; c, ten days after operation; d, forty-three days after operation.

essentially to normal on the sixteenth day after operation and remained so until the dog was killed (Fig. 4, dog 5).

*Necropsy.*—Dog 4 was killed two and a half months after operation. The pericardium had been opened, and was slightly adherent over the right ventricle and the upper posterior third of the left ventricle. There was no evidence of myocardial infarction. The endocardium and valves were normal.

Dog 5 was killed ten months after operation. The pericardium had been opened and was adherent by fine bands over the right ventricle and the adjacent anterior fourth of the left ventricle. Careful study of the heart revealed no evidence of myocardial infarction. The endocardium and valves were normal.

*Control experiment 3.*—Another type of control experiment was performed in which the pericardium was not opened, but in which the pericardial ligaments were severed and the heart was vigorously manipulated (dog 6). Negative T-waves of



low amplitude were present in all three leads in the normal preoperative tracing. There was no change in the RS-T levels in the electrocardiogram taken immediately after operation under ether. The T-wave in Lead I became positive on the afternoon following operation and remained so until the eleventh day after operation. The T-wave in Lead II was positive on the fourth day, was positive and exaggerated on the fifth day, and negative on the ninth day. The tracing returned to normal on the fifteenth day after operation.

*Necropsy.*—Dog 6 was killed two months and five days after operation. There were no pericardial adhesions. The myocardium, endocardium and valves were normal.

#### COMMENT ON CONTROL EXPERIMENTS AND THEIR RELATION TO LIGATION EXPERIMENTS

1. Sharp, deep inversions of the T-waves may follow opening of the pericardium and manipulation of the heart without ligation of any

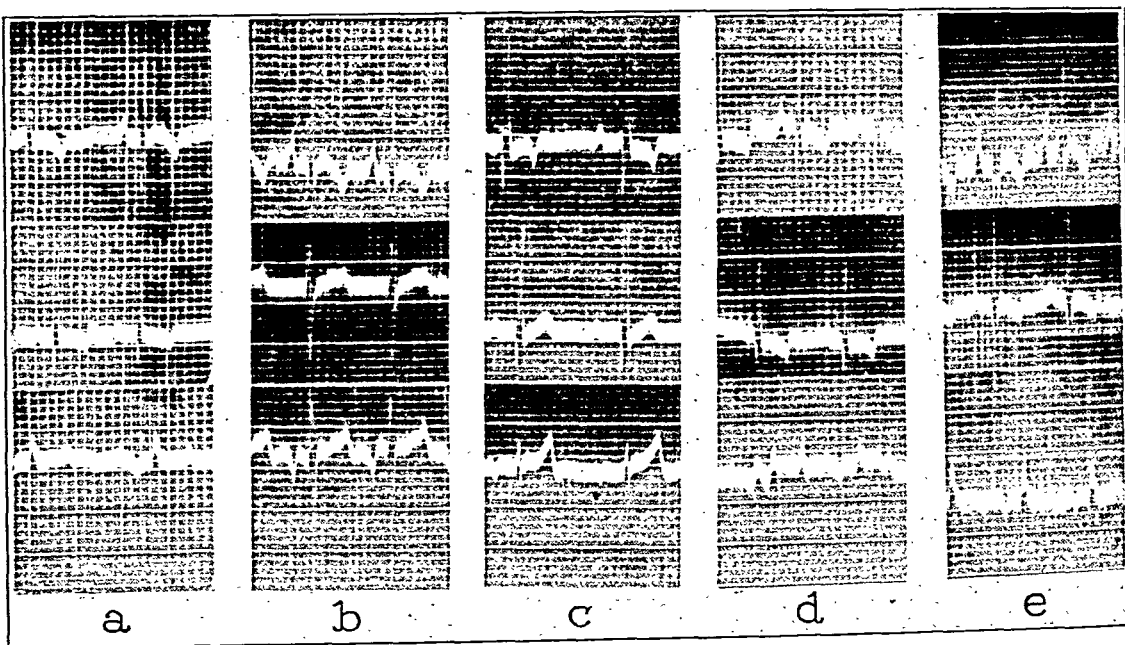


Fig. 4.—Dog. 5. The pericardial sac was opened but the coronary arteries were not ligated. The electrocardiograms were taken as follows: a, before operation; b, the afternoon following operation; c, seven days after operation; d, sixteen days after operation; e, seven and three-fourths months after operation.

coronary vessels. Under the conditions of our experiments it is evident that reversal of the direction of the T-waves only cannot be considered a manifestation of the effects of coronary obstruction.

2. There is a late stage in which T-wave negativity is replaced by positive T-waves which may arise from the descending limb of the R-wave and become greatly exaggerated. This change usually occurs in the combined Leads I and II or II and III, and is transitory in character, occurring from the fourth to the twenty-fifth day, although it may begin earlier and last longer.

3. There is more tendency for the T-waves to become reversed in direction and to maintain the reverse direction in the final electrocar-

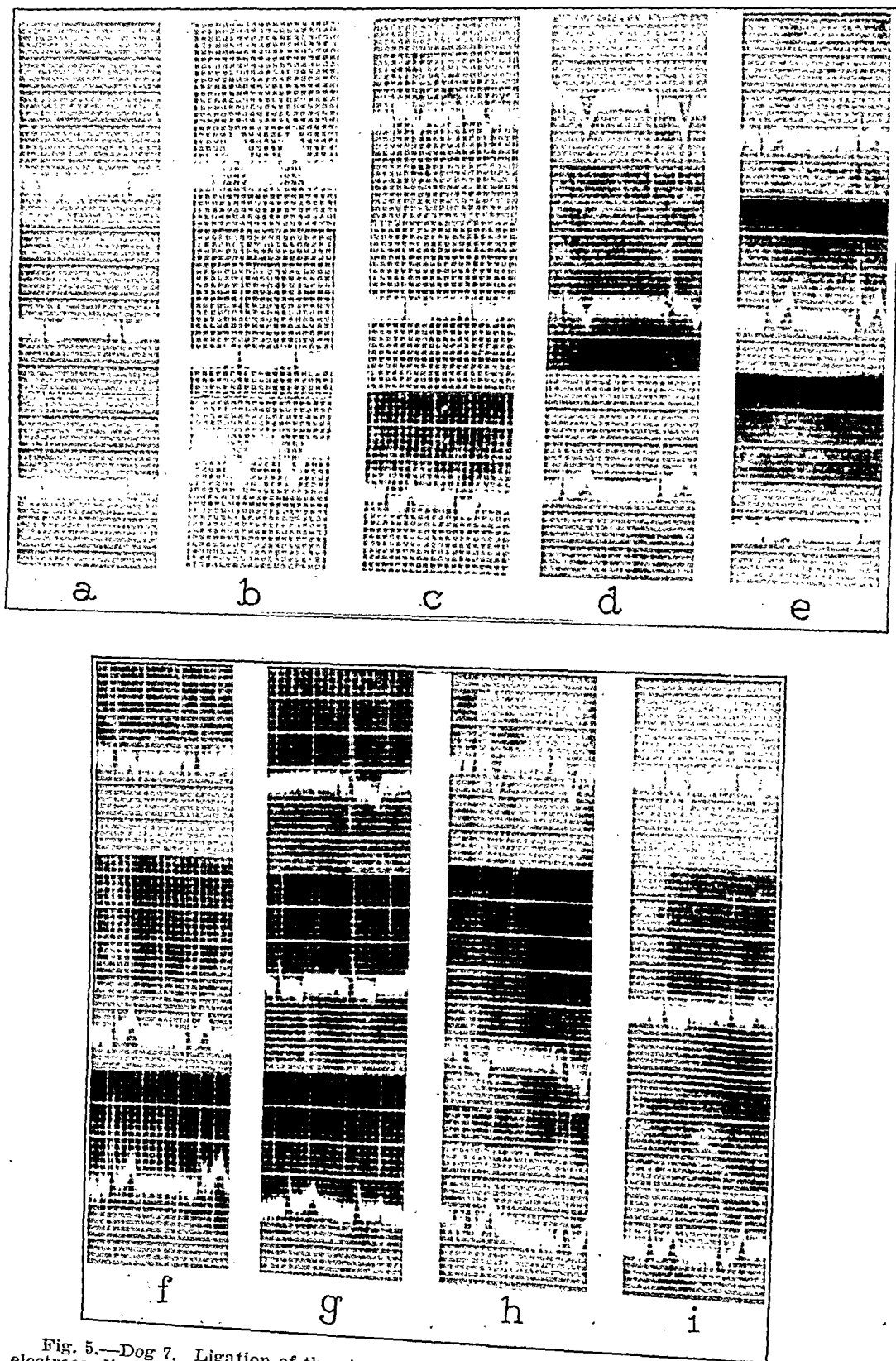


Fig. 5.—Dog 7. Ligation of the circumflex division of the left coronary artery. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation with the dog under ether anesthesia; *c*, the afternoon following operation; *d*, two days after operation; *e*, eleven days after operation; *f*, thirteen days after operation; *g*, twenty-two days after operation; *h*, ninety-five days after operation; *i*, two hundred seventy-five days after operation.

diagrams of dogs in which the T-wave is sharply upright in Lead I in the original tracing. In dogs in which the T-wave in Lead I is negative in the tracing taken before operation, there is a distinct tendency for the tracings to return to normal after the period during which the T-waves become positive and exaggerated, as has been described.

4. In these control experiments no significant modifications of the level and contour of the RS-T segment occur in the electrocardiograms taken under ether, immediately after operation or during the remainder of the day.

With this knowledge of the electrocardiographic changes produced by opening the pericardium and manipulating the heart, but not interfering with the coronary circulation, one is in a position to recognize the effects of ligation of the coronary arteries. First the effects of ligation of the branches of the left coronary artery will be considered.

*Ligation experiment 1 (left coronary artery).*—The posterior division of the circumflex branch of the left coronary artery of dog 7 was ligated. In the electrocardiogram taken immediately after operation, while the dog was still anesthetized, was seen the high origin of the T-wave from the descending limb of the R-wave, with marked positivity of the R-T segment in that lead (Fig. 5). In Lead III there is marked fusion of the S- and T-waves resulting from low take-off of the T-waves. In Lead II the T-wave has become almost iso-electric. In the tracing taken in the afternoon following operation, with the dog fully awake, a negative T-wave is present in Lead I with a persistently high take-off of the T-wave, or, in other words, an elevated R-T segment. The S-T segment in Lead III was still markedly depressed, but the T-wave in Lead III had become sharply upright. Auricular fibrillation was present one day after operation, and the RS-T segments in Leads I and III retained similar, although slighter, changes to those just described. The changes in the level of the RS-T segments disappeared after the first day. Then followed increased negativity of the T-wave in Lead I, which was interrupted by positivity and exaggeration of the T-wave first in Leads I and II, and later in Leads II and III. From the twenty-second day, until the dog was killed, negativity of  $T_1$  and  $T_2$ , and positivity of  $T_3$  persisted. One is tempted to consider the sharply negative T-wave in Lead I, and the sharply positive T-wave in Lead III, observed at the end of the experiment, as a manifestation of infarction, the exact counterpart of which is seen in the late stage of the electrocardiogram of man when the apical and anterior portion of the left ventricle is the seat of infarction.<sup>3,6</sup> However, these same changes were observed in the control experiments (Fig. 1); therefore an interpretation such as that suggested is open to doubt.

*Necropsy.*—Dog 7 was killed eleven months after operation. At necropsy, the pericardium was adherent over various portions of the right ventricle, but adhesions to the left ventricle were not present to any extent, except over the region of infarction. A large, white area occupied the posterior portion of the left ventricle, immediately adjacent to the posterior interventricular septum. This area had a maximal width of 1.5 cm. and extended from 0.75 cm. from the base almost to the apex. The adjacent portion of the right ventricle was not involved, and there was only slight involvement of the posterior interventricular septum. The cardiac muscle was completely replaced in this area by scar tissue which had a thickness of about 2 mm. The myocardium of the remainder of the left ventricle, and of the right ventricle, was normal. No gross abnormalities of the endocardium or valves were noted.

*Ligation experiment 2 (left coronary artery).*—In dog 8 a branch of the circumflex division of the left coronary artery supplying the posterior and basal portion of the left ventricle was ligated. Here again was obtained a high origin of the T-wave from the R-wave, with a positive, convex, R-T component following operation (Fig. 6). There was slight upward convexity of the R-T segment in Lead II. In Lead III there was fusion of the S- and T-waves, with low origin of the T-wave from the S-wave in that lead. The subsequent changes were practically the same as those observed in control experiment 2 (Fig. 3).

*Necropsy.*—Dog 8 was killed ten months after operation. The pericardium was adherent, by scattered bands, over the entire right ventricle and the basal half of the left ventricle. The pericardium was very firmly adherent at the site of infarction, which was in the posterior basal portion of the left ventricle, 1.5 cm. from the base, and 1 cm. from the posterior interventricular septum. There was a depressed scar at the area of infarction measuring 1 by 1.5 cm., with a slightly greater area on the endocardial surface, and infarction involved the anterior papillary

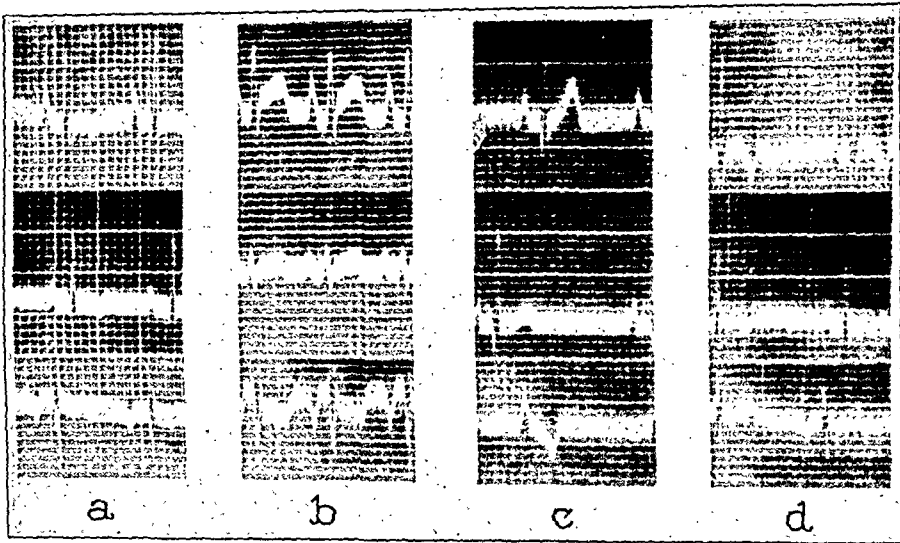


Fig. 6.—Dog 8. Ligation of a branch of the circumflex division of the left coronary artery. Electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation under ether anesthesia; *c*, ten days after operation; *d*, seventy-four days after operation.

muscle. At the central portion of this scar, practically the entire thickness of the left ventricle consisted of fibrous tissue. In the valves, endocardium, and remaining part of the myocardium, there were no gross abnormalities.

*Ligation experiment 3 (left coronary artery).*—In dog 9, the posterior descending branch of the circumflex division of the left coronary artery was ligated. In the electrocardiogram taken immediately after operation, while the dog was anesthetized, the T-wave in Lead I took its origin high on the R-wave; the T-wave in Leads I and II showed increased negativity, and there was marked fusion of the S- and T-waves in Lead III, with low origin of the T-wave from the S-wave (Fig. 7). These changes in the RS-T segment were present in the tracings taken in the afternoon following operation and one day following operation. The reciprocal relation of  $T_1$  and  $T_2$  is clearly shown in the fact that as  $T_1$  became more negative,  $T_2$  became more positive and acute. The dog died the second day after operation.

*Necropsy.*—Death of dog 9 resulted from hemorrhage from a small branch of the anterior descending division of the left coronary artery. A ligature was found about the posterior descending branch of the circumflex artery at a distance of about 0.7 cm. from the coronary sulcus. Injection of the circumflex branch disclosed an

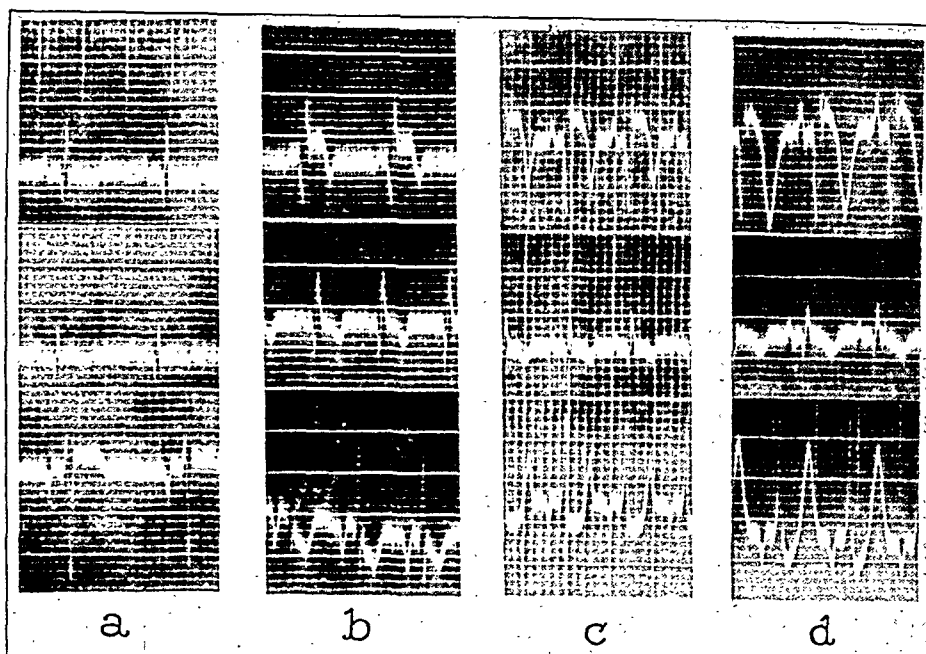


Fig. 7.—Dog 9. Ligation of the posterior descending branch of the circumflex division of the left coronary artery. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after the thorax was closed under ether anesthesia; *c*, the afternoon following operation; *d*, the day following operation.

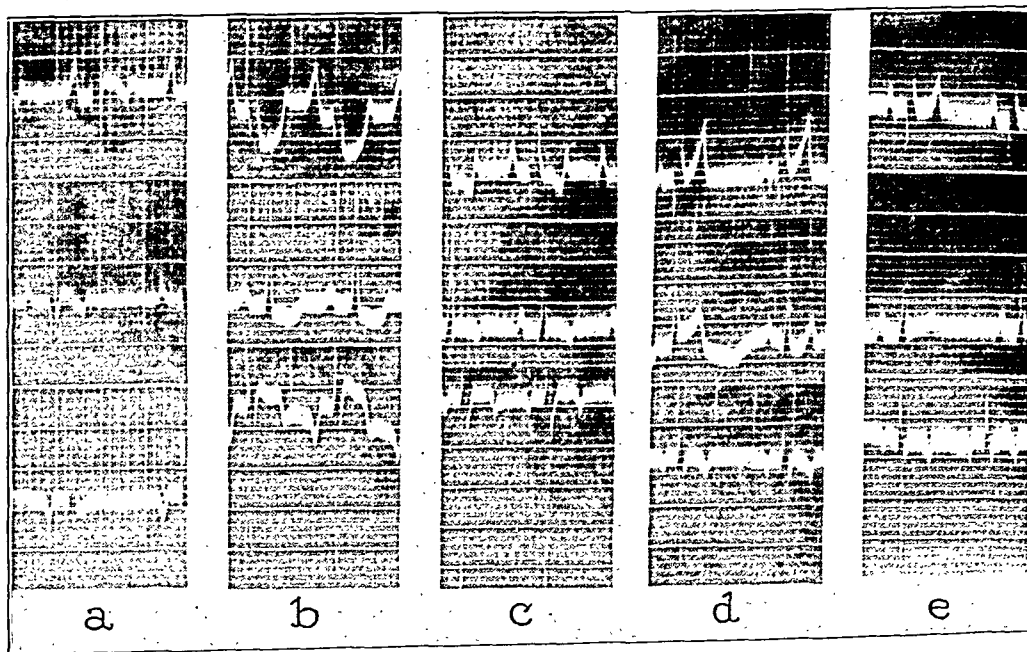


Fig. 8.—Dog 10. Ligation of two branches of the left coronary artery supplying the right ventricle. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation with the dog under ether anesthesia; *c*, the afternoon following operation; *d*, ten days after operation; *e*, two hundred one days after operation.

ischemic area below this point, to within 0.5 cm. of the apex. This area extended about 1 cm. anterior to the posterior insertion of the interventricular septum and occupied the posterior portion of the left ventricle. The endocardium and valves were normal.

In another dog (not numbered and not examined post-mortem) following ligation of two anterior branches of the circumflex division of the left coronary artery, an elevated convexity of the R-T segment occurred in Lead I, without a high take-off of the T-wave from the R-wave. Similarly, a depressed S-T segment occurred in Lead III, without a low take-off of the T-wave from the S-wave. These changes were present in the electrocardiogram taken on the day following operation and subsequently. There appeared on the third day a peculiar, convex, upward rounding of the R-T segment in Leads I and II, with slightly high origin of these segments from the R-wave. This is probably to be considered a preliminary step to the development of positive and exaggerated T-waves in those leads if the dog had lived.

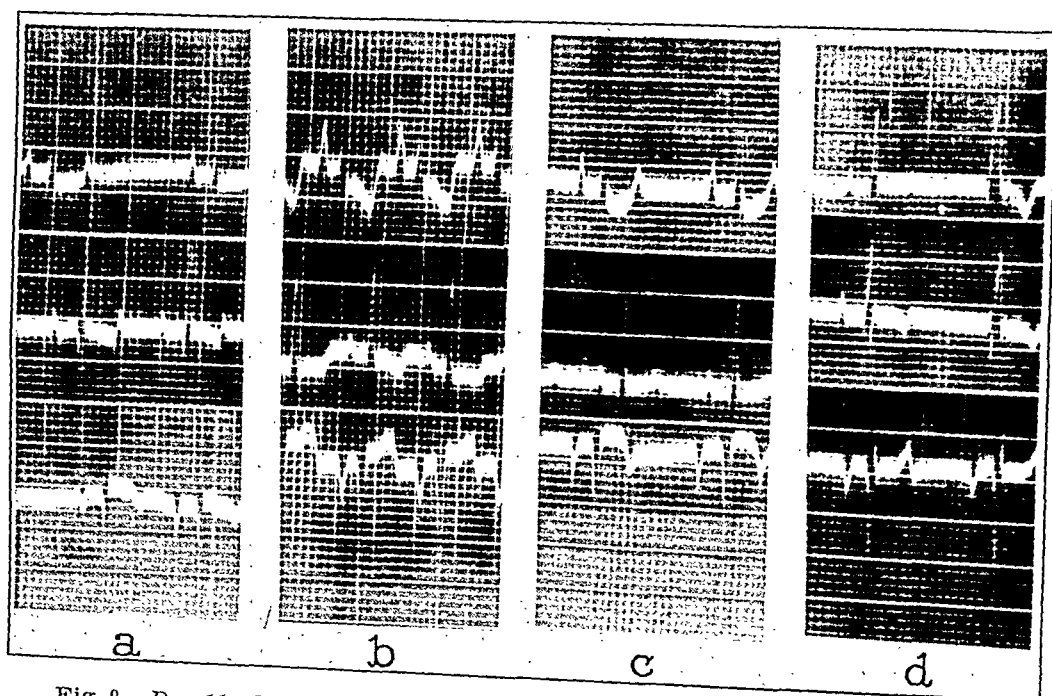


Fig. 9.—Dog 11. Ligation of a branch of the right coronary artery supplying the right ventricle. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation under ether anesthesia; *c*, the afternoon following operation; *d*, two days after operation.

In a control experiment in which all the steps of the experiment were carried out except ligation of coronary vessels, such changes in the R-T segments in Leads I and II appeared on the fifth day, and were followed by development of greatly exaggerated positive T-waves in those leads on the ninth day.

*Ligation experiment 4 (right coronary artery).*—In dog 10, two branches of the right coronary artery, supplying the middle portion of the right ventricle, were ligated. In the electrocardiogram taken immediately after the thorax was closed, with the dog under ether, we observed marked fusion of the S- and T-waves in Lead I with very low origin of the T-wave in that lead (Fig. 8). There was slight depression of the S-T segment in Lead II. The S-T segment in Lead III was markedly positive, with an upward rounded contour. This change was present, although in a much smaller degree, in the tracing taken on the afternoon following operation. Then the transitory phase of positive, exaggerated T-waves, with elevated take-off in Leads I and II, appeared, as were observed in control experiments. However, in this experiment, the exact reversal of the T-waves in the final tracings, as

compared to the original tracing, persisted to the end. We did not see this in control experiments in which we started with a negative T-wave in Lead I (Figs. 3 and 4). Inasmuch as the final electrocardiographic changes in this dog were such as would be observed in the late stage of infarction involving the posterior basal portion of the left ventricle in the heart of man, it is possible that they may be ascribed to infarction of the right ventricle. However, one is prevented from positively attributing them to infarction when it is recalled that such a reversal of the direction of the T-waves was obtained in a control experiment in which the T-wave was positive in the original tracing (Fig. 1).

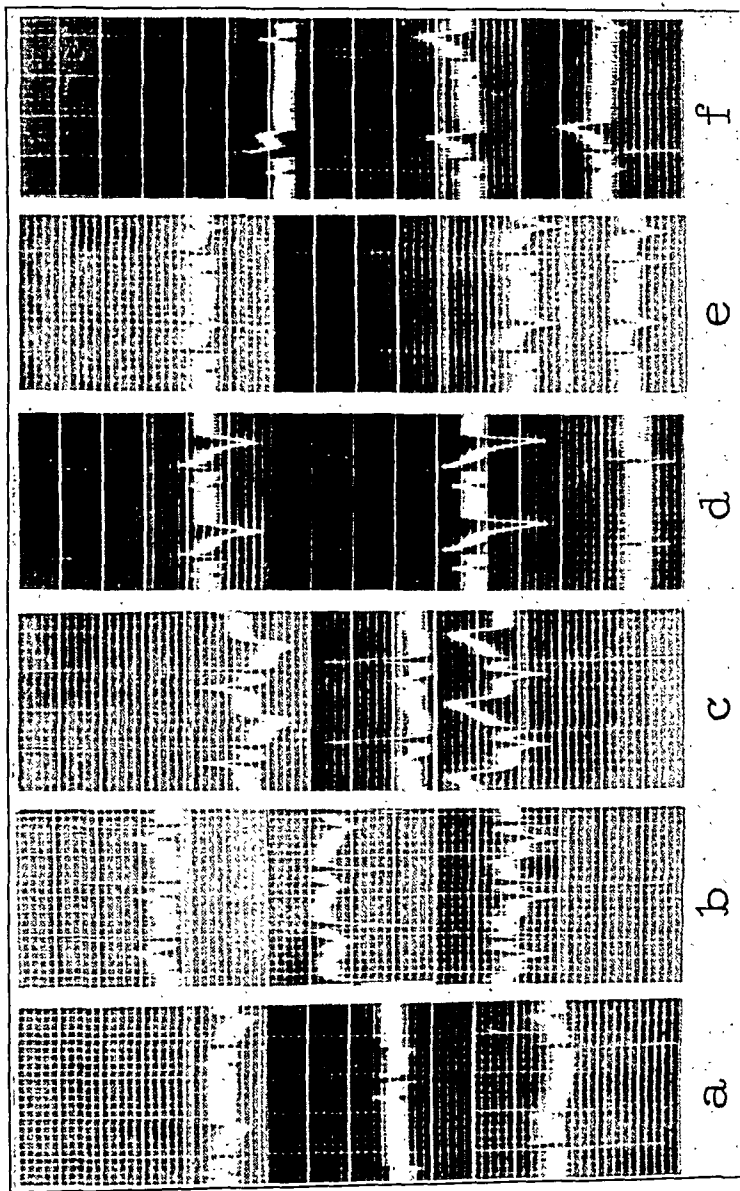


Fig. 10.—Dog 12. A branch of the right coronary artery, supplying a portion of the right ventricle, was ligated. Electrocardiograms were obtained as follows: *a*, before operation; *b*, before operation under ether anesthesia; *c*, immediately after operation under ether anesthesia; *d*, one day after operation; *e*, five days after operation; *f*, nine days after operation.

*Necropsy.*—Dog 10 was killed eight months after operation. At necropsy, pericardial adhesions were observed across the base of the right ventricle. The middle portion of the right ventricle was the seat of infarction, and was grayish in color. The infarct began about 0.5 cm. from the base, and spread out over a fan-shaped area, toward the apex of the right ventricle. This area was thinned. The fibrosis was largely confined to the epicardial half of the myocardium. The left

ventricle was thickened and apparently hypertrophied. The valves and endocardium of the remaining portion of the heart were normal.

*Ligation experiment 5 (right coronary artery).*—In dog 11, a branch of the right coronary artery to the right ventricle was ligated. In the electrocardiogram taken before operation there was slight depression of the S-T segment in Lead I, and slight elevation of it in Lead III (Fig. 9). In the electrocardiogram taken immediately after operation the depression of the S-T segment in Lead III was likewise accentuated. These changes persisted in lesser degree in the electrocardiogram taken in the afternoon following the operation. Two days after operation there was marked negativity of the T-wave in Lead I, and the T-wave in Lead III had become positive and exaggerated. The dog died four days after operation.

*Necropsy.*—Dog 11 died on the fourth day after operation. At necropsy, a ligature was found about the branch of the right coronary artery in the mid-basal portion of the right ventricle. There was a bluish discoloration of the pericardium spread out over the surface of the right ventricle, distal to this ligature, measuring 2 by 4 cm. The corresponding area on the endocardial surface had a bluish-red appearance. This was found to be an area of acute hemorrhagic infarction.

*Ligation experiment 6 (right coronary artery).*—A branch of the right coronary artery to the right ventricle was ligated in dog 12. In the electrocardiogram taken immediately after operation on the etherized dog, fusion of the S- and T-waves in Lead I, with depression of the S-T segment in that lead was seen (Fig. 10). The S-T segment had a high take-off in Lead III, with marked exaggeration and increased positivity of the T-wave in that lead. The R-T segment in Lead II was slightly depressed. The changes in the RS-T segment persisted definitely in Leads I and III in the afternoon, but disappeared thereafter. Then appeared, on the fourth day, an elevated take-off of the T-wave in all leads, which resulted, finally, in exaggerated positive T-waves in all leads. These positive T-waves persisted until the fifteenth day. It is well to recall that similarly exaggerated positive T-waves were to be observed in the tracings following control experiments, so that these changes are not regarded as a manifestation of the results of ligation of the coronary vessels.

*Necropsy.*—Dog 12 died one month after operation. On opening the pleural cavity it was found to be filled with blood-tinged fluid. There was an extensive, fibrinous exudate practically covering the heart, and that could be separated from it with difficulty. A grayish area occupied the middle portion of the right ventricle, and measured about 1.5 by 2 cm. This portion of the myocardium was markedly thinned. When viewed on its endocardial surface, the area was distinctly paler than the adjacent muscle. Microscopic section disclosed that this was an area of partially healed infarction. The endocardium, valves, and muscles of the remainder of the heart were not abnormal.

#### GENERAL COMMENT

In biological experiments it is always difficult to reproduce conditions in an animal that correspond exactly to those existing in man. In the dog the circulation, the distribution of the conduction system, the structure of the mediastinum, the angle that the heart makes with the various axes of the thorax, the influence of the vagus nerve, and the degree to which the right ventricle enters into the formation of the base of the heart may differ from those of man. It is not surprising, therefore, that the normal electrocardiogram of the dog differs so markedly from the normal electrocardiogram of man. It has been mentioned previously that the T-wave of the electrocardiogram of the



normal dog may be negative in Lead I, in Leads I and II, in Leads I, II and III, or in Lead III alone, and that the changes in the T-waves observed following our experiments varied according to the nature of the T-wave in the normal tracing.

The most important step in any investigation is the control experiment. We found that reversal of the direction of the T-waves could occur as a result of completion of all the steps of the experiment except ligation of the coronary vessels. So it became apparent that reversal of the direction of the T-waves following ligation of the coronary vessels could not be accepted unreservedly as a characteristic feature of infarction with the conditions under which our experiments were performed. This observation throws doubt on any investigation similarly performed in which the production of such a reversal of the direction of the T-waves is regarded as a manifestation of myocardial infarction in the dog. Moreover, the control experiments established the fact that the peculiar, exaggerated, positive T-waves produced usually in two leads, from the second to the twenty-fifth or fortieth day after operation, were not waves peculiar to experiments in which the coronary vessels were ligated. These results do not invalidate in any way the observations in man that reversal of the direction of the T-waves, and exaggeration and increased positivity of the T-waves, may occur as a result of coronary occlusion. However, it must be remembered that the conditions in coronary occlusion in man and those present in our experiments, at least in their later stages, are quite different. Under experimental conditions we have opened the pericardium, and whether we leave it open or suture it, there is likely to be a certain pericardial reaction leading commonly to adhesions over the various portions of the heart. We have to deal, then, with the effects on the electrocardiogram of inflammatory reactions, and what is probably more important, with the fact that adhesions occurring asymmetrically over the heart can modify the cardiac axes with reference to the various electrocardiographic leads. Moreover, the circulatory adjustments following obstruction of a coronary vessel in the face of the normal circulation of a dog cannot completely duplicate conditions following obstruction of a coronary vessel in the heart of man, the remainder of whose coronary circulation is usually seriously injured. Comparative anatomy suggests that the Thebesian circulation plays a more important part in the lower animals than it does in those higher in the biologic scale.<sup>21</sup>

After allowance is made for all the changes that are observed under the conditions of the control experiments, there is yet one important type of electrocardiographic change observed to occur after ligation of the coronary vessels. This has to do with modifications of the RS-T component of the electrocardiogram appearing immediately after operation, and usually disappearing in from a few hours to twenty-four hours after operation. This is most clearly manifested in Leads I and

III. Moreover, it is seen that these changes are characteristically different and opposite in type for infarction in the left and the right ventricle respectively. When a branch of the left coronary artery distributed exclusively to the left ventricle is ligated, producing infarction of the ventricle, in the tracing taken immediately after operation, origin of the T-wave from the R-wave in Lead I is high, and the R-T segment may take on a rounded, positive convexity. With this there may develop a very sharp, deep, negative T-wave in Lead I. In Lead III, on the contrary, there is fusion of the S- and T-waves with a low take-off from the S-wave, producing a trough-like depression of the S-T segment. If the dog fails progressively, and dies within twenty-four to forty-eight hours after operation, this change may persist to the end. However, if a branch of the right coronary artery is ligated, producing infarction in the right ventricle, in the tracing taken immediately after operation a high origin of the T-wave from the R-wave in Lead III is observed, producing a positive, convex, R-T segment in that lead, with or without negativity of the T-wave. In Lead I, fusion of the RS-T segment is observed, with a low take-off of the T-wave from the R- or S-wave, leading to a trough-like depression of the RS-T segment. It will be observed, also, that the T-waves in Leads I and III tend to act reciprocally; that is, as the T-wave in Lead I undergoes inversion, the T-wave in Lead III becomes positive, sharp, and exaggerated; whereas, when the T-wave becomes negative in Lead III, the T-wave in Lead I tends to become more positive and sharper. The changes observed in Lead II do not obey any definite or predictable pattern, and clearly indicate the advantages of including Leads I and III of the electrocardiogram in any study of the effects of experimental coronary occlusion.

Mention has been made of the fact that these changes in the RS-T components of the electrocardiogram disappeared in a few hours, except in an instance in which the dog progressively failed until its death on the second day after operation. At first glance, this might be considered as indicating that these changes were not due to myocardial injury. However, Otto<sup>16</sup> observed a similar rapid decrease in the degree of changes in the RS-T segment produced by injecting 95 per cent alcohol into the cardiac muscle. Smith<sup>18</sup> also observed that the increased prominence of the T-wave, observed immediately after ligation, was replaced in twenty-four hours by a sharply negative T-wave. It appears possible that the condition produced in the myocardium of the dog following coronary ligation or chemical injury results in changes in the RS-T segment of the electrocardiogram which undergo readjustments more rapidly than they do in the human heart. Were it practicable, at this point we should like to review for comparison the duration of the changes in the RS-T segment, observed in the electrocardiogram of man following myocardial infarction,<sup>4, 17</sup> as pointed out by Parkinson and Bedford<sup>17</sup> and by Barnes.<sup>4</sup> What is more important, probably, is the fact that those electrocardiographic changes

that occur independently of infarction, and observed in our control experiment, namely, reversal of the direction of the T-waves and their positive exaggeration in one or more leads, appear early, and they obscure the modifications in the RS-T segment.

This study clearly indicates that infarction in one ventricle produces electrocardiographic effects which are characteristic and opposed to effects produced by the other ventricle. The work of Eppinger and Rothberger,<sup>8</sup> and Otto,<sup>14, 16</sup> indicated that this was true for axial leads. Our investigations do not answer the question as to whether infarctions of various portions of the same ventricle of the dog produce dissimilar electrocardiographic changes. This question seems definitely answered in the negative by the findings of the investigators last mentioned.

Are these changes in the RS-T segment, following infarction, the result of electropotential forces of the right and of the left ventricle, which are antagonistic because the right ventricle occupies a right basal position, whereas the left ventricle constitutes the left and apical portion of the heart? Are they linked up with the fact that the conduction system to the right and left ventricles of the heart are separate, and that injury anywhere within the region supplied by one side of the conduction system produces a characteristic change? Or are these changes related, in some fashion, to the fact that injury in the region of the myocardium supplied by one coronary artery produces a characteristic electrocardiographic picture? It seems fairly certain that we can answer the last two questions in the negative by referring to the results observed in infarction in the heart of man. In man acute infarction at the posterior basal portion of the left ventricle produces changes in the RS-T segment that are characteristic, and that are opposed to those produced by infarction in the anterior and apical portions of the left ventricle.<sup>4, 6</sup> In man, also, the same branch of the conduction system supplies both regions of infarction, and the electrocardiographic changes are the same following acute infarction of the posterior basal portion of the left ventricle, regardless of whether it is supplied by the right or the left coronary artery.<sup>6</sup> A number of experimental observations seem to oppose the idea that infarction in the right ventricle of the dog produces opposite effects on the RS-T segment from infarction in the left ventricle, by virtue of the fact that the right ventricle occupies a basal position in the heart with reference to the left ventricle. The experiments of Eppinger and Rothberger, and of Otto, indicate that injury to any part of the left ventricle produces the same type of electrocardiographic change. In the injury to one ventricle, Eppinger and Rothberger found that when changes in the RS-T segment occurred they were all of a similar type, although differing in degree, and Otto arrived at a similar conclusion. It was found, also, that injury of the left half of the septum, no matter at what level, produced the same type of RS-T change as did injury of any other portion of the left ventricle, whereas, similar injury of the

right half of the septum produced an RS-T effect that was no different from that produced by injury of any portion of the right ventricle.<sup>8</sup> Moreover, Otto<sup>14</sup> found that ligation of the anterior descending branch of the left coronary artery supplying the anterior portion of both the right and the left ventricles, adjacent to the interventricular septum, produced electrocardiographic changes which partook partly of the character of those produced by injury of the left ventricle, and partly of those produced by injury of the right ventricle. The available evidence seems to indicate that so far as effects on the RS-T component of the electrocardiogram are concerned, the dog's heart may be conceived of as being divided by a plane fairly accurately separating the right and left ventricles. Such a separation does not appear to exist in the heart of man.<sup>6</sup>

Is cardiac dilatation essential to the production of fusion of the RS-T segment following experimental occlusion of coronary arteries of the dog? The transitory character of the changes in the RS-T segment which we obtained, and their tendency to persist until failure and death twenty-four to forty-eight hours after operation, might be in harmony with such an observation. Further experiments to induce cardiac dilatation following experimental obstruction of coronary vessels, and determination of the effects of these combined procedures on the RS-T segment of the electrocardiogram should throw light on this question.

The investigations of Feil, Katz, Moore and Scott<sup>9</sup> indicate that ligation of the descending branch of the left coronary artery alone does not produce modifications of the RS-T segment of the electrocardiogram characteristic of infarction, in dogs that are allowed to survive sixty-eight minutes or less after the coronary ligation. These investigators were able to produce such changes in the RS-T segment only if, in addition to ligation of the descending branch, they obstructed the inferior vena cava. They felt that the marked fall in mean blood pressure with followed obstruction of the vena cava, and the increasing anoxemia thus produced, were necessary factors in production of the changes in the RS-T complex in the electrocardiogram. In this connection it is well to recall that the descending branch of the left coronary artery in the dog supplies not only the anterior portion of the left ventricle, but the interventricular septum and the adjacent portion of the right ventricle as well. In axial leads, Otto noted that closure of the right coronary artery had a negative influence on the T-wave of the electrocardiogram; closure of the circumflex division of the left coronary artery had the opposite effect, and closure of the anterior division tended to produce both effects; that is, "the T-wave began before the complete ascent of S, yet its peak became more positive." He explained the latter result by the fact that the zone of discoloration which followed ligation of the descending branch occupied a position over the lower portion of the anterior interventricular groove and

apex, midway between the right ventricle above and anteriorly, and the left ventricle to the left and posteriorly. This might explain why Feil and others obtained changes in the RS-T segment characteristic of infarction of the right ventricle in some instances, due to involvement predominantly of the right and basal portion of the heart, and in other instances evidences of infarction of the left ventricle, due to involvement predominantly of the left and posterior portion of the heart. In other words, the area of ischemia in the dog's heart produced by ligation of the descending branch of the left coronary artery may be a relatively neutral zone. It may give rise to opposed electrical effects of right and left ventricular origin, making it somewhat difficult to obtain changes in the RS-T component characteristic of infarction. When such changes are obtained, they may not be constant in all animals.

#### CONCLUSIONS

1. Infarction of the right ventricle produced by ligation of branches of the right coronary artery in the dog induces characteristic changes in the RS-T component of the electrocardiogram. These changes are distinctly different from those following infarction in the left ventricle produced by ligation of branches of the left coronary artery.

2. These characteristic changes are best appreciated only when one studies Leads I and III of the electrocardiogram.

3. The changes in the RS-T segment observed following acute infarction of the left ventricle of the dog closely resemble the early changes in the RS-T segment following acute infarction of the anterior apical portion of the left ventricle of man.

4. The changes in the RS-T segment observed following acute infarction of the right ventricle of the dog closely resemble the early changes in the RS-T segment following acute infarction of the posterior basal portion of the left ventricle of man.

5. The reversal of the direction of the T-wave and the occurrence of exaggerated positive T-waves in one or more leads could not be considered to be a result of infarction, inasmuch as these same changes were observed to occur in similar experiments in which the same procedures were carried out except that no coronary vessels were ligated.

6. The available evidence indicates that so far as their effects on the RS-T segment of the electrocardiograms are concerned, the right and the left ventricle of the dog each acts as a unit. This behavior does not seem to be explained wholly by the fact that the right ventricle occupies a more basal position than the left ventricle.

7. Control experiments in evaluating changes following experimental occlusion of the coronary vessels in the dog are important.

8. It is impossible to secure strictly comparable conditions in myocardial infarction following experimental occlusion of the coronary vessels in dogs and following spontaneous closure of the coronary vessels in man.

9. The character and direction of the T-wave in the normal electrocardiogram of the dog differ from the same features of the normal electrocardiogram of man. The changes of the T-wave in the dog following identical experimental procedures appear to vary according to the character and direction of the T-wave in the normal electrocardiogram.

10. The last two conclusions probably explain why it is difficult to interpret, and probably not possible to reproduce, in dogs, the late changes in the electrocardiogram as seen in man following myocardial infarction.

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## AURICULAR FLUTTER AND FIBRILLATION SHOWING VARYING BLOCK ASSOCIATED WITH CHEYNE- STOKES RESPIRATION\*†

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IT IS well known that changes in sinus rate occur during Cheyne-Stokes respiration. The subject is fully discussed by Wenckebach and Winterberg.<sup>1</sup> Usually it is found that the sinus rate slows during the hyperpneic stage and speeds up during the apneic period. The change is due as a rule to a central action of the vagus, which alters the activity of the sinus node. We have found no notation in the literature of the appearance of block in Cheyne-Stokes breathing, either with sinus rhythm, auricular flutter or auricular fibrillation. For this reason an unusual case is described in which Cheyne-Stokes breathing occurred during sinus rhythm, auricular flutter and auricular fibrillation with, at times, striking variation, sometimes halving, of the ventricular rate during auricular flutter due to synchronous changes in A-V block paralleling the hyperpneic and apneic periods.

### CASE REPORT

*History.*—S. G., aged thirty-nine years, married, was admitted to the Meyer House on January 28, 1931, complaining of dyspnea, cough, and insomnia of a month's duration with edema of the ankles for the past two days. There was a definite history of recurrent attacks of rheumatic fever at the ages of nine, eleven and fourteen years. In July, 1929, he suffered from an attack of streptococcus sore throat during which he complained of attacks of severe precordial pain. A diagnosis of pericarditis with effusion was made at this time.

On admission he was kept at rest in bed and given morphine. Fluids were limited to 1000 c.c. per day, and he was kept on a high caloric, high carbohydrate diet. He was also slowly digitalized and finally became fully compensated in about ten weeks, when he was discharged in relatively good condition. Two electrocardiograms were taken at this time (Fig. 1 *A* and *B*), showing notching of QRS and in the second record some prolongation of A-V conduction time, up to 0.22 sec.

On April 8, 1931, he was again admitted to the hospital in a state of advanced congestive heart failure. He was again put on a régime of rest, high carbohydrate diet and fluid restriction. Pantopon, gr. 1/3, was given when needed. Digitalis was given for a period of seven days and was then refused by the patient. During digitalis medication auricular fibrillation developed, which was followed by auricular flutter. Quinidine sulphate was administered over a period of five days, 2 grams in all being given, during which the mechanism was restored to the sinus rhythm.

*Physical Examination.*—The patient was an adult, white male of about forty years, well developed and well nourished. He was orthopneic, dyspneic, and had a characteristic mitral flush of the cheeks. His lips, tongue and ear lobes were cyanotic. The thyroid gland was not palpably enlarged. The veins of the neck were distended,

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pulsating and filled from below. The lungs presented dullness and crepitant râles at the bases. The apex beat was palpated in the sixth interspace, at the left anterior axillary line. There were a precordial heave and a systolic precordial purring thrill. The right heart border was percussed 4 cm. from the midsternal line and the left heart border in the left anterior axillary line. Presystolic and systolic murmurs

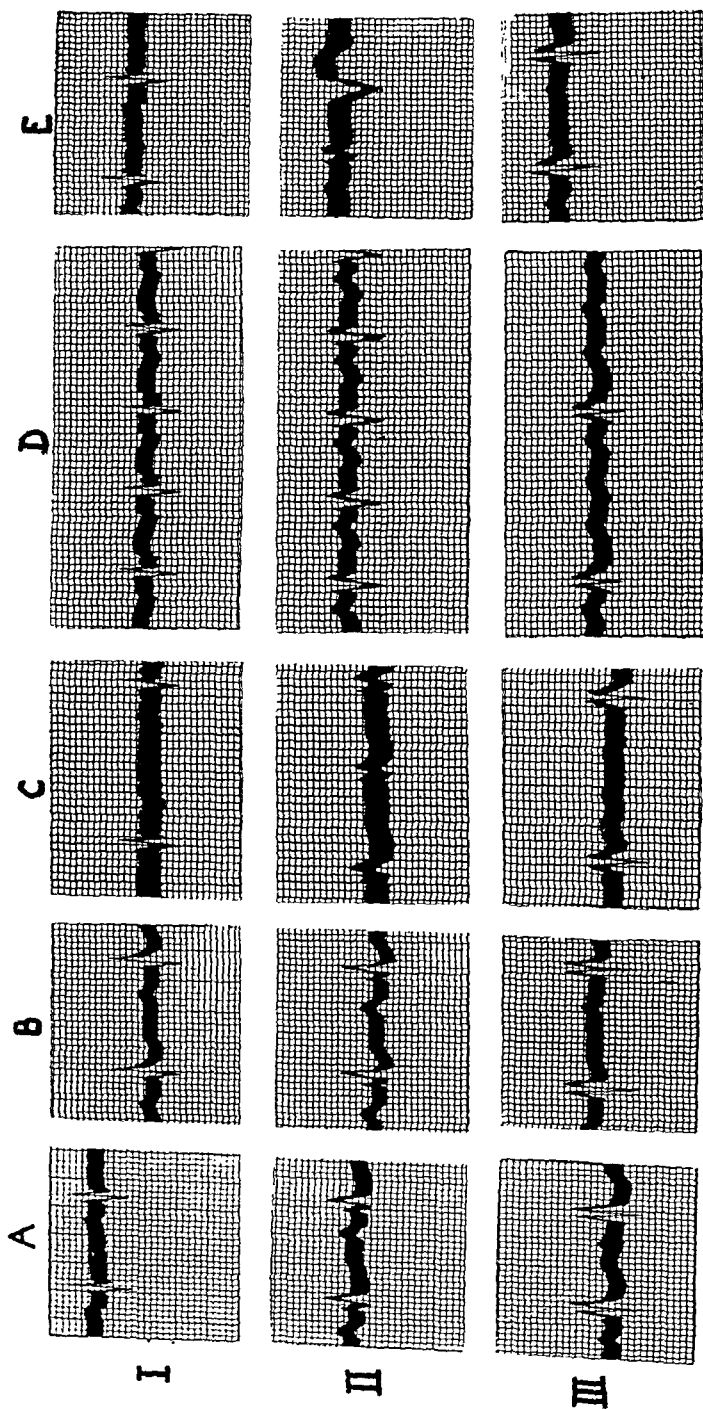


Fig. 1.—Segments from electrocardiograms taken on January 24, *A*; on February 2, *B*; on April 15, *C*; in the morning of April 28, *D*, Leads I and II during apnea and Lead III during hyperpnea; and on May 12, *E*.

were heard at the apex and a diastolic murmur was heard over the aortic area. The second aortic sound was louder than the second pulmonic. The liver edge was felt four fingerbreadths below the costal margin; the organ did not pulsate and was slightly tender. The flanks bulged and a fluid wave was elicited. Capillary pulsation, Corrigan pulse, and a Duroziez murmur were noted. The legs showed moderate pitting edema. The reflexes were not abnormal.



The diagnosis on admission was rheumatic heart disease, cardiac hypertrophy and dilatation, mitral insufficiency and stenosis, aortic insufficiency, sinus rhythm, Class III.

*Progress.*—The physical examinations showed essentially the same condition on both admissions. The progress of the first stay in the hospital has been summarized in the history. During the first stay in the hospital there was a persistent regular sinus rhythm and no evidence of Cheyne-Stokes breathing.

On the second entry on April 8 the patient was rapidly digitalized. The electrocardiograms on April 15 (Fig. 1 C) showed coarse auricular fibrillation, whereas on the previous day frequent premature contractions were demonstrated clinically. A sinus mechanism was restored in a few days. On April 18 he had a short attack of apnea, and three days later Cheyne-Stokes respiration set in which persisted until his death; a gallop rhythm was also noted at this time. During the same day he had an attack of severe orthopnea, vertigo, tinnitus, and motor aphasia. The next day he had a right-sided hemiparesis with hemianesthesia and right homonymous hemianopsia, with continuance of the aphasia. The neurological diagnosis by Doctor L. J. Pollock was "vascular accident to the internal capsule." The intracranial lesion progressively improved, and the pulse continued to be regular. On April 27, it was noted that the pulse was slow during the hyperpneic phase and rapid during apnea; this was confirmed by an electrocardiogram (Fig. 1 D) taken on the next day, which showed that the mechanism was a flutter of the auricles with 2:1 block during apnea and 4:1 block during hyperpnea. Later that afternoon another record was taken which showed coarse auricular fibrillation with varying block associated with Cheyne-Stokes respiration. Quinidine medication was started on April 29, a total of 2 grams having been taken by May 1, after which time it was refused. Electrocardiograms taken on May 9 and 12 (Fig. 1 E) showed a return to normal sinus mechanism with no respiratory variation of the rate as was previously noted, and only an occasional ventricular extrasystole.

The patient ran an afebrile course until April 22 when for a period of eight days there was fever, the highest level reached being 102° F. The temperature then subsided until May 6 when it started to rise and remained elevated, reaching the level of 105.4° F. at the end. The apneic periods became progressively longer and the pulse very thready. He died on May 15. A postmortem examination was not done.

*Laboratory Data.*—Roentgenogram of the chest showed the transverse heart diameter to be 20.5 cm. and the transverse chest diameter, 30.5 cm. A small amount of fluid in both costophrenic angles was present.

The basal metabolic rates were +50.2 per cent on February 11, and +13.0 per cent on February 14. Blood chemistry on January 29 showed sugar, 101 mg. per 100 c.c.; nonprotein nitrogen, 38 mg. per 100 c.c. On April 24, sugar was 95 mg. per 100 c.c.; nonprotein nitrogen, 43 mg. per 100 c.c.; creatinine, 2.1 mg. per 100 c.c. A blood culture was negative on two weeks' growth. Urinalysis showed four-plus albumin, occasional red and white cells, and coarsely granular casts. A blood count on April 9 showed R.B.C., 4,440,000; Hb., 75 per cent, and W.B.C., 8,200. On April 26 the W.B.C. count was 10,600. The blood pressure varied between 150/0 and 270/0 mm. Hg.

#### COMMENT

The electrocardiograms show definite evidence of intraventricular block of the so-called "aborization type" (cf. Fig. 1). The QRS is small in amplitude, prolonged to 0.12 of a second, and notched deeply. In Lead I it is chiefly directed downward; in Lead II, in most records, it is directed upward, but in Fig. 1 D it is mainly downward; in Lead III

the direction is more variable. The T-wave is small or not discernible, viz., in Fig. 1 *C* and 1 *E*; it is upright in Lead III and inverted in Lead I. In most instances the S-T segment is negative in all leads or at least in Leads II and III. The change from a sinus rhythm to coarse auricular fibrillation, then to auricular flutter and back to a sinus rhythm is shown in Fig. 1. A ventricular extrasystole is seen in Lead II of Fig. 1 *A* and *E* and 0.22 sec. in Fig. 1 *B* indicating the presence in the latter record of first-stage A-V block.

The flutter record of Fig. 1 *D* was taken during Cheyne-Stokes breathing, Leads I and II during the apneic and Lead III during the hyperpneic stage. The flutter waves are clear and regular at a rate of

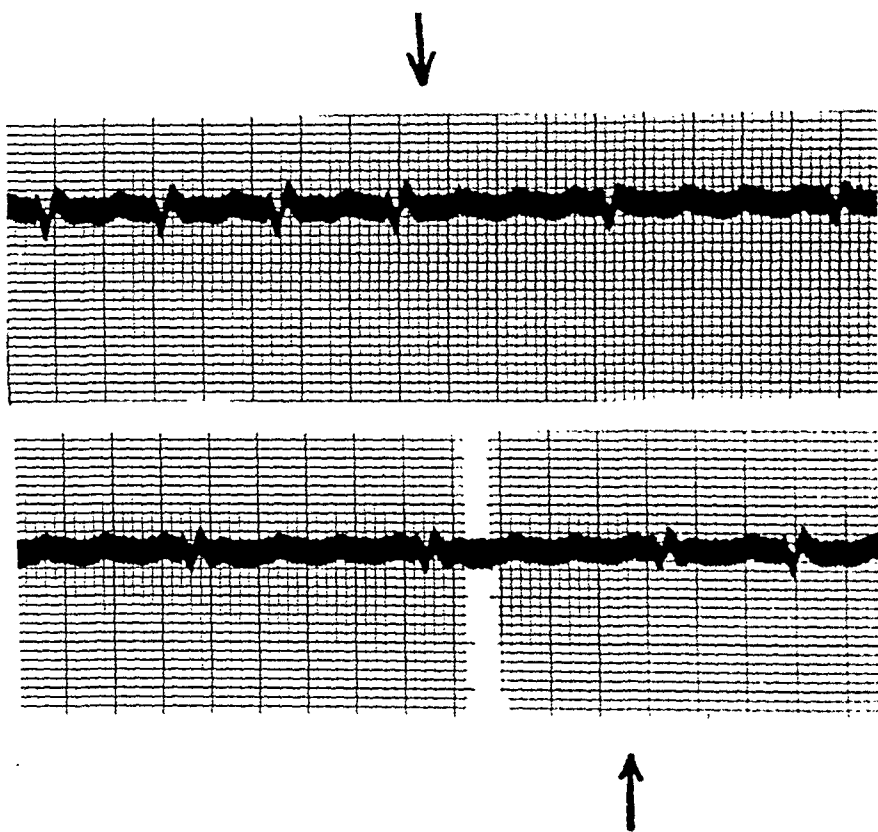


Fig. 2.—Electrocardiogram, Lead II, taken April 28, A.M., showing auricular flutter with transition from 2:1 to 4:1 block and back, during various phases of Cheyne-Stokes breathing. ↓ shows onset of hyperpnea, ↑ shows end of hyperpnea.

250 per minute. During apnea there is 2:1 A-V block; during hyperpnea the block is increased to 4:1. The transition from 2:1 to 4:1 block and back is shown in the two segments in Fig. 2 selected from a long strip of Lead II taken at the same time as the record in Fig. 1 *D*. It was observed that the transition from 2:1 to 4:1 block occurred when apnea ended and the transition from 4:1 to 2:1 block occurred when apnea began. The change in A-V block was unaccompanied by any change in the flutter rate.

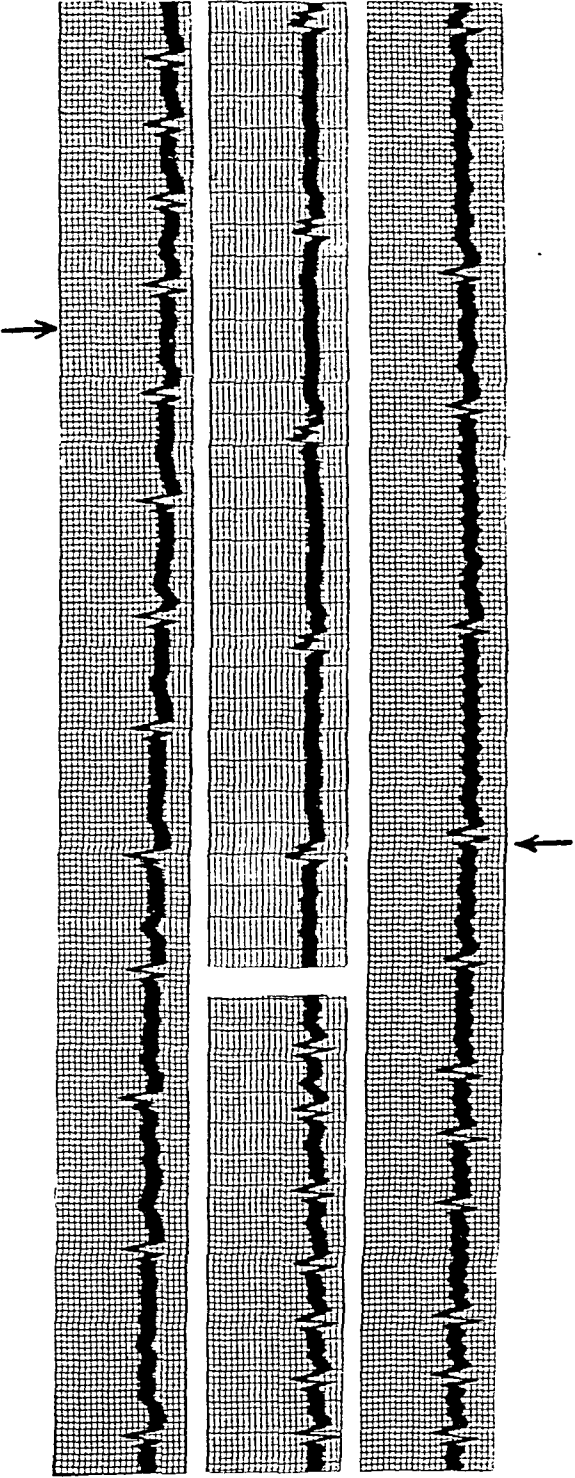


Fig. 3.—Electrocardiogram, Lead II, taken April 28, p. m. In upper strip is shown decrease in A-V block during the apnea, (↓ shows onset of apnea); the mechanism is a coarse auricular fibrillation. In middle two strips, is seen the development of complete A-V block during hyperpnea, the mechanism being coarse auricular fibrillation. In lower strip is seen increase in A-V block during hyperpnea, onset of which is shown by ↑. Note the change in the flutter waves from a double wave to a notch which eventually disappears.

The same afternoon a continuous record was taken during several cycles of Cheyne-Stokes breathing; a record of the respiratory activity being taken simultaneously with the electrocardiogram to time the changes in the latter more accurately. During this long record the auricles were alternating between coarse auricular fibrillation as in the two upper strips of Fig. 3 and auricular flutter as in the lower strip of Fig. 3. The lower strip shows the flutter rate to be 300. During the apneic phase (early part of strip) the flutter waves are split in two, and there is 2:1 and 4:1 block. When the patient began to breathe, the doubling of the flutter wave changed after a short lag to a notch which became less and less distinct at the same time the A-V block increased to 4:1 and 7:1 block. This change was not associated with any change in the flutter rate. In the middle strip is shown the coarse auricular fibrillation with the rapid irregular ventricular rate averaging 143 beats seen in apnea, and the slow regular ventricular rate of 45 seen during hyperpnea, which is probably a complete A-V block with the idioventricular rhythm located in the A-V node, as is borne out by the change in the appearance of the QRS complex. The auricular oscillations are irregular in spacing and amplitude and not very clear. In the top strip is shown the more gradual transition in A-V block as the apneic stage replaced the hyperpneic.

When the record of Fig. 1 *E* was taken, a long strip of Lead II was made during the Cheyne-Stokes breathing. The irregularity in breathing was less marked than when the records of Figs. 2 and 3 were taken, and no significant change in sinus rate or P-R interval was found.

This case is unusual in that Cheyne-Stokes breathing produced no cyclic changes in sinus rate nor, apparently, any cyclic change in the rate of auricular flutter and fibrillation. The variations in ventricular rate which occurred during the periods of auricular flutter and fibrillation were due to marked alterations in the A-V block. During the period of auricular flutter the block changed from 2:1 during apnea to 4:1 during hyperpnea in one instance; during a period of coarse auricular fibrillation complete A-V block developed in the hyperpneic period of Cheyne-Stokes breathing. The change in block synchronized with the change in the character of breathing. The increase in A-V block during the hyperpneic period can be explained by a spread of impulses from the hyperactive respiratory center to the closely adjoining cardioinhibitory center, an explanation which has been advanced to explain the sinus bradycardia during hyperpnea in Cheyne-Stokes breathing (Wenckebach and Winterberg<sup>1</sup>). On the other hand the increased A-V block may be due to some chemical change in the blood, such as the anoxemia and hypercapnia, which produce the cyclic modification in the respiratory center activity (Haldane<sup>2</sup>), acting simultaneously on the cardioinhibitory center. The studies of Resnick<sup>3</sup> on the effects of anoxemia on

A-V conduction would suggest that the chemical changes in the blood might produce their effect directly on the A-V node. The evidence is inconclusive as to which mechanism operated in this case.

#### SUMMARY

An unusual case is reported in which the A-V block accompanying auricular flutter and coarse auricular fibrillation varied markedly during Cheyne-Stokes breathing, in one instance leading to a complete A-V block during the hyperpneic stage. Hyperpnea in this case increased the A-V block and apnea decreased it without any apparent effect on the rate of flutter or fibrillation of the auricles.

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# EXPERIMENTAL BUNDLE-BRANCH BLOCK IN THE CAT

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THE electrocardiographic distinction between right and left bundle-branch block in human beings has been associated with considerable confusion. The classification of Lewis and his coworkers,<sup>1, 2</sup> based largely upon their experimental work on dogs, found for a time almost universal acceptance. However, Fahr<sup>3</sup> in 1920, chiefly on theoretical grounds, came to the conclusion that electrocardiograms ascribed to right bundle-branch block by Lewis actually represented left bundle-branch block, and vice versa. Barker, Macleod and Alexander,<sup>4</sup> in a remarkable study of the excitatory process in an exposed human heart, developed evidence strongly suggestive of the latter view. More recently Mann<sup>5</sup> and Wilson, Macleod and Barker,<sup>6</sup> using entirely different methods, re-analyzed the original records of Lewis and came independently to a conclusion opposite to his.

Since most of the confusion is due to curves Lewis obtained by cutting or clamping the main branches of the bundle in dogs, we have repeated the work on cats.

## METHOD

Nineteen cats were used, the anesthetic being sodium amytal injected intraperitoneally (75 mg. for an adult cat). Needle electrodes were placed under the skin and tied. The chest was opened, artificial respiration established and the whole heart exposed by slitting the pericardial sac; the control electrocardiogram being taken after this step. A cataract knife, the handle of which had been replaced by an oval shank of much smaller diameter, was used to produce the desired lesion.

In the first six experiments the knife was introduced into the ventricular cavity by way of the auricular appendage, while in the remaining thirteen it was inserted directly through the ventricular wall. Using the direct or ventricular route, the right branch was cut by inserting the knife through the anterior wall near its junction with the septum, just below the pulmonary cusps. After it was introduced a short distance into the ventricular cavity nearly parallel to the auriculoventricular groove, it was slowly withdrawn with the cutting edge directed against the septum so as to transect the main branch in its course to the anterior papillary muscle. In the left ventricle the knife was inserted through the outer wall on the left side, near the ventricular base. The cutting edge was directed toward the septum, the anterior cusp of the mitral valve cut and then a slit made on the upper portion of the septum just below and parallel to the base of the aortic valve. If the electrocardiogram taken after the initial attempt showed no change from the normal (as was frequently the case), the knife was reinserted through the ventricular wall and another cut made.

In the case of the indirect or auricular route, a brass cannula was inserted into the ventricle by way of the auricle and the auricular appendage tied around it.

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Then the knife was introduced into the ventricle through the cannula, the bore of which fitted the knife handle. In the right ventricle the knife was directed into the ventricular cavity until it nearly touched the junction of the anterior wall and septum at a point just below the pulmonary cusps. It was then withdrawn with the cutting edge against the septum and a slit made so as to transect the main branch also in its course to the anterior papillary muscle. In the left ventricle the cutting edge of the knife was directed toward the upper portion of the septum, and after transection of the anterior cusp of the mitral valve, a slit was made on the septal wall just below and parallel to the base of the aortic cusps.

Following the initial attempt, the blade of the knife was withdrawn into the lumen of the cannula and an electrocardiogram taken. If the latter showed no change from the control, the operation was repeated. After the desired lesion was produced, tracings were taken at frequent intervals over a prolonged period of time to demonstrate the permanency of the change. Although both methods yielded satisfactory results, the auricular route seemed to be preferable for the left ventricle and the ventricular route for the right.

All specimens were examined postmortem and the cuts verified. The main right branch is readily seen as a grayish-white strand in its course to the anterior papillary muscle, and if the slit transected the branch, it was obvious to the naked eye without having to resort to microscopic investigation. The main left branch is not so visible but is identifiable below the junction of the right and posterior aortic cusps. A slit parallel to the cusps and just below them usually transected the main branch before its division into its sub-branches.

#### RESULTS

Twelve successful experiments were performed, in six of which the right division of the bundle of His was cut and in the remaining six the left. Other experiments were done in which varying degrees of trauma were seen on the opposite side of the septum to the ventricle into which the knife had been introduced. All these, even those in which this damage was minimal, were ruled out with one exception. In that case (cat 15) complete heart-block was produced in addition to left bundle-branch block. However, as there was no evidence of damage to the right ventricle in the region of the right division but only to the main bundle at a higher level, it seemed justifiable to include this experiment in the series. It may be mentioned that in all the discarded experiments in which no considerable damage was done to the opposite side of the septum, the results supported those described below.

Control electrocardiograms taken after the introduction of the knife into the ventricle before transection of the division showed no significant change from the normal. Even in those cases in which post-mortem examination revealed some deep as well as superficial cuts, none of which had transected either of the main branches, but all of which had caused considerable damage to the endocardium and myocardium of the septum, no gross change in the form of the electrocardiogram was produced. This latter observation has been previously made by Eppinger and Rothberger<sup>8</sup> in their work on the hearts of dogs.

Typical electrocardiograms of both the discordant and the concordant type, using these terms in the same sense as they were employed by

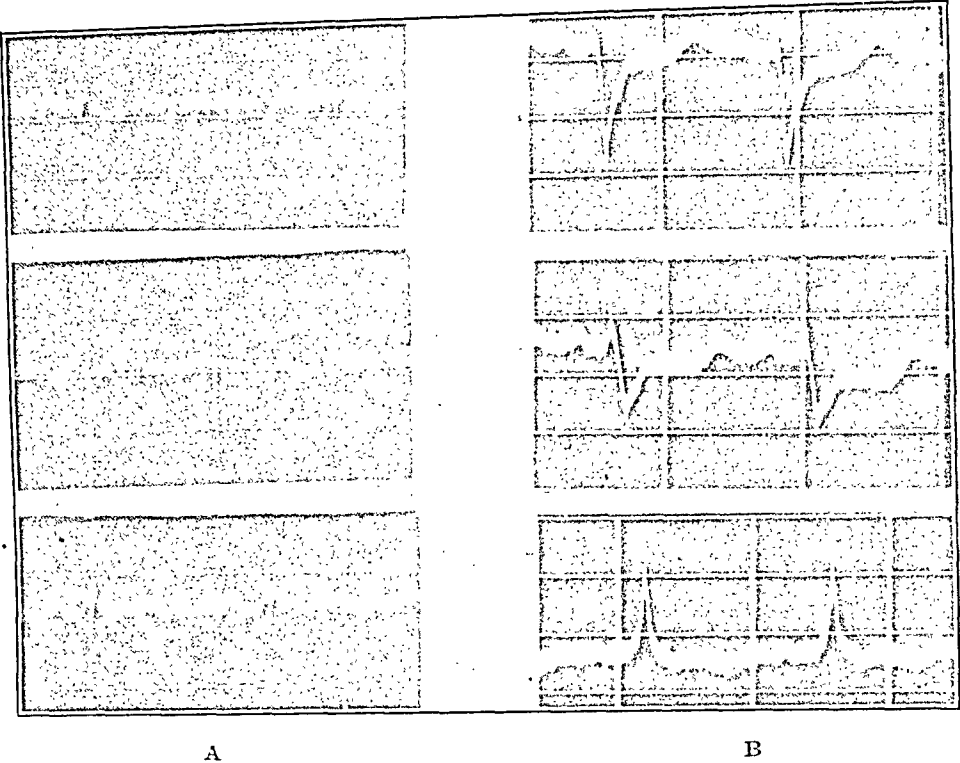


Fig. 1.—A, Normal. B, Right division cut. Discordant type. Time, one-fifth second. 1 cm. = 1 millivolt.

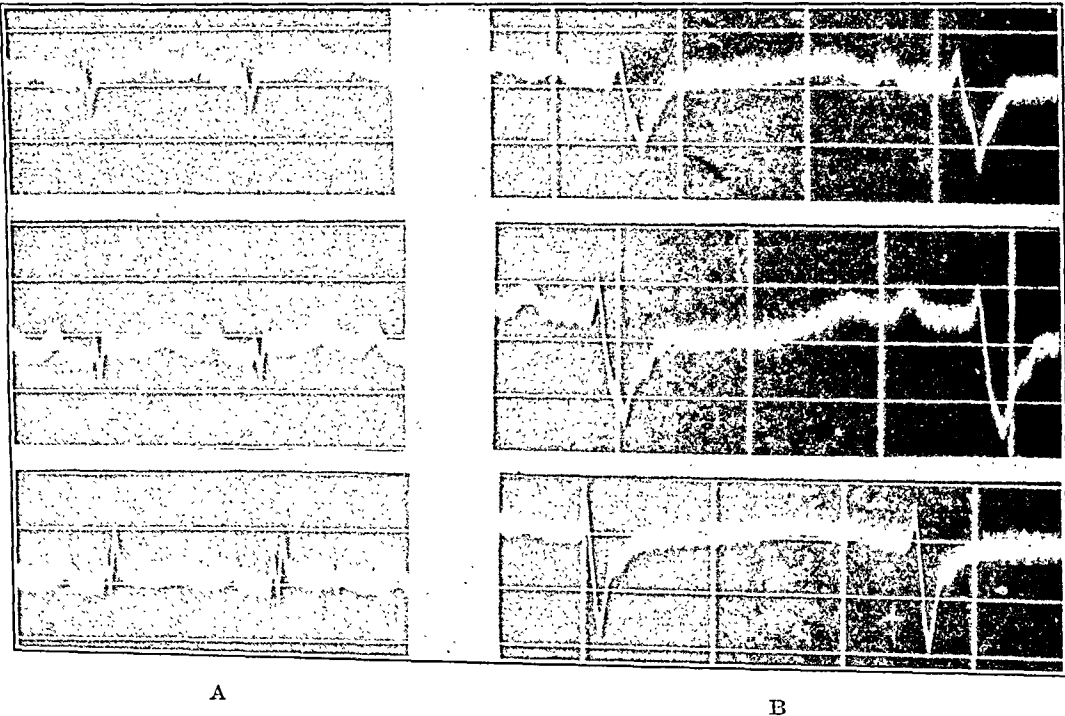


Fig. 2.—A, Normal. B, Right division cut. Concordant type.





Lewis, are illustrated. Tables have been constructed of the successful experiments in which the amplitude (expressed in one-tenth millivolts) of the main deflections in the control electrocardiograms are compared with those obtained after cutting one of the divisions of the bundle.

In order to avoid repetition it can be stated that all curves taken after the transection of a division showed a marked widening of the QRS complex.

*Right Division Cut (Table I. Figs. 1 and 2).*—In these experiments a very high grade of bundle-branch block, in many cases complete, was obtained in every instance. In four (cats 1, 6, 10, 17) the curves were discordant and in two (cats 9, 19) concordant.

Lead I. In each case the chief initial deflection was the S-wave. In three no R-wave was present, while in the other three R was of small amplitude. In five experiments T was positive, i.e., opposite to the chief initial deflection, while in the remaining one it was iso-electric.

Lead II. In every instance the chief initial deflection was the S-wave, while T was positive. The curves thus resembled those in Lead I.

Lead III. In four experiments the chief initial deflection was R. In these S was practically absent. In one (cat 9) the chief deflection was S, which made the curves concordant. This was the only instance in which S was higher in Lead III than in Lead I. In another (cat 19) R was slightly larger than S, but the time interval of S was much greater than R; hence it seemed that those curves should also be considered concordant. T was of low voltage in every case. In three it was slightly negative, i.e., opposite to the chief deflection, in two slightly positive, and in the remaining one isoelectric.

*Left Division Cut (Table II. Figs. 3 and 4).*—In three experiments a complete block of the division was produced while in the others the block was of high grade. In one instance auricular fibrillation took place during the experiment, which of course did not affect the ventricle except as to rate and rhythm. Two experiments gave markedly discordant curves (cats 15, 16), two slightly discordant (cats 3, 14), while the other two were slightly concordant (cats 4, 11).

Lead I. In every instance the chief deflection was R. In no experiment was S present, while T was always negative, i.e., opposite to the chief deflection.

Lead II. In all the experiments the chief initial deflection was R. In none was S seen, while T was negative except in one case. The curves resembled those in Lead I.

Lead III. In four experiments the chief initial deflection was S. In two of these (cats 15, 16) R was almost absent, while in the other two (cats 3, 14) a definite R was seen, although its voltage was less than S. In another instance (cat 4) R and S were equal, while in the remaining one (cat 11) R was slightly greater than S. In the latter the normal curve showed an R of very low voltage in Lead I while in Lead III its amplitude was high, with S absent in both leads, i.e., some right axis



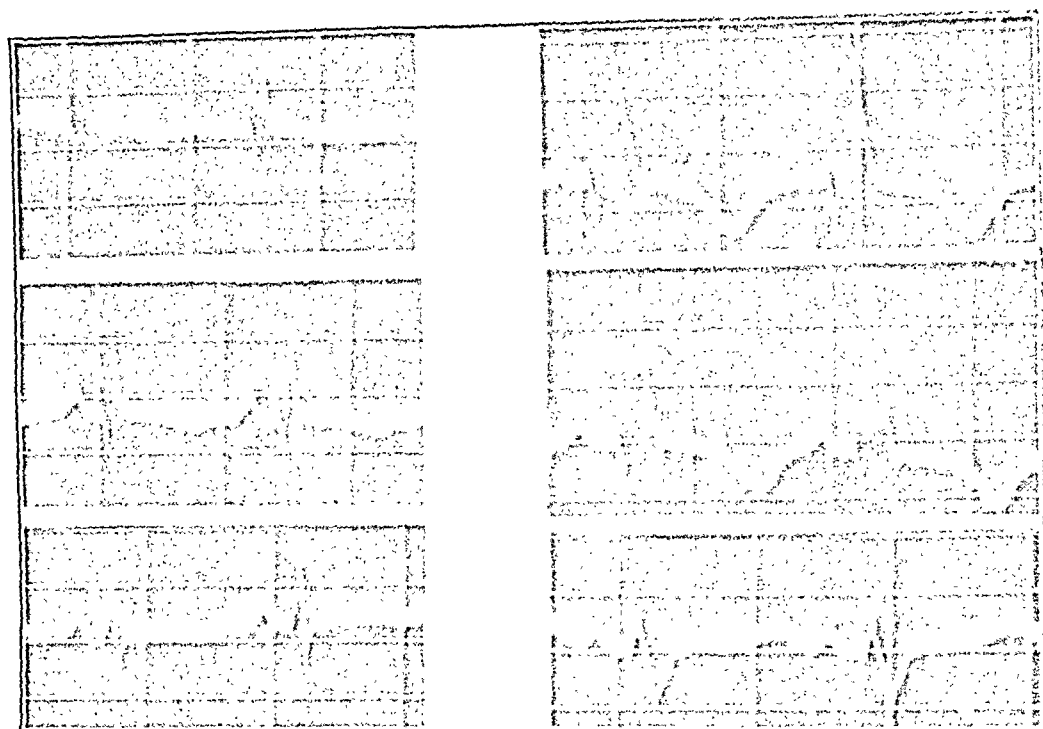


Fig. 3.—A, Normal. B, Left division cut. Decoplant type.

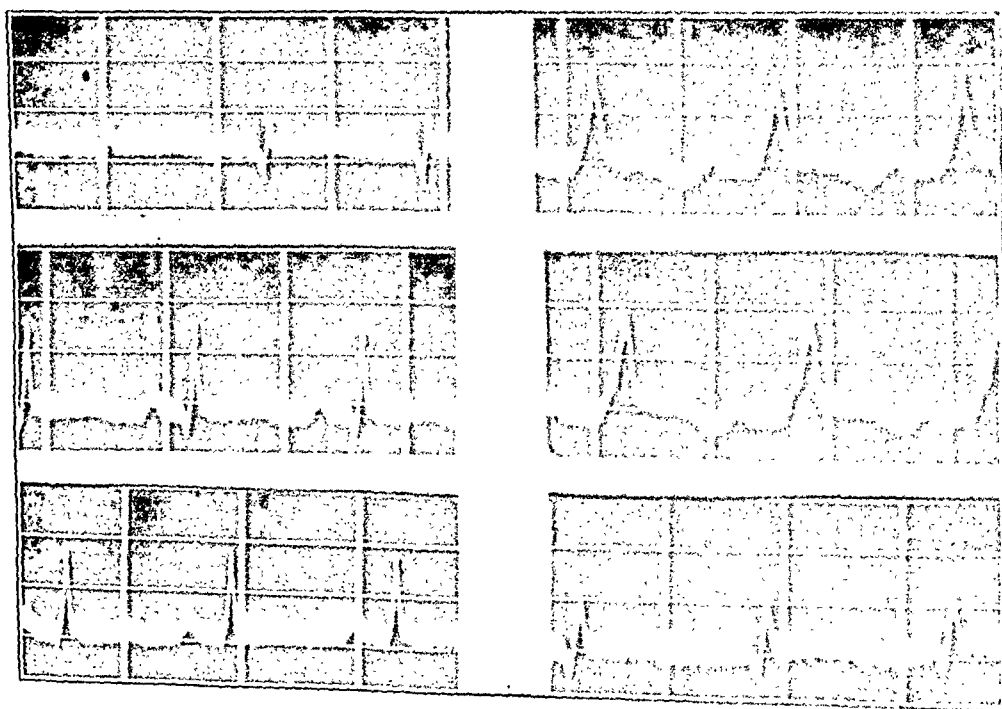


Fig. 4.—A, Normal. B, Left division cut. Concordant type.

deviation. This was the only case in which the normal curves showed a much greater amplitude of R in Lead III than in Lead I. In none of the concordant tracings was the amplitude of R in Lead III as great as that in Lead I. In two experiments T was slightly positive, in two slightly negative and in the other two iso-electric.

#### DISCUSSION

The interpretation of the initial phases of human bundle-branch block curves advanced by Lewis is based upon anatomical consideration and the order of ventricular activation as determined in the dog and assumed to be similar in the human. Wilson<sup>6</sup> and Mann<sup>5</sup> have both pointed out that the conclusions derived from experiments on the canine heart should not be so applied without taking into consideration the marked differences between canine and human hearts in regard to the position of the anatomical axes and the angle of the interventricular septa. Wilson has criticized Lewis' analysis of the discordant levocardiograms obtained by the latter in a small percentage of dogs because surface readings were taken from hearts in which the form of the levocardiogram was not investigated and compared with the electrical axis calculated from a discordant levocardiogram, a type known to be exceptional in the dog. Furthermore, the position of the canine heart with respect to the three standard leads varies from that of the human, and there is also a material difference in the distribution of the sub-branches of the right division of the bundle. Large and important strands of conduction tissue which bridge the cavity of the dog's right ventricle are not found in man.

Barker and his collaborators,<sup>4</sup> given an extraordinary opportunity to study the excitatory process in an exposed human heart, stimulated various points on the surface of the two ventricles and simultaneously recorded the three standard leads. All the curves obtained from the right ventricle showed upward chief initial deflections in Lead I, while all those from the left ventricle were in the opposite direction. They further found that as the superior aspect of the heart was approached Leads II and III tended to become inverted, indicating that the form of the electrocardiogram of a ventricular extrasystole is dependent upon both the Purkinje system, right or left, to which it first spreads, and the level at which it enters the system. Available evidence indicates clearly that the form of a right ventricular extrasystole resembles the curve of left bundle-branch block and vice versa. Their concordant curves (chief deflections all in the same direction) supported the conclusions arrived at by Lewis with regard to bundle-branch block, but their discordant curves (chief deflections opposite in Leads I and III) were in complete disagreement with his findings. Our results in the cat agree with those of Barker and his coworkers. Whether the curves obtained were discordant or concordant, division of the right main branch resulted in the

chief deflection in Lead I being downward, while after division of the left branch the chief deflection in Lead I was upward.

Wilson and Herrmann<sup>9</sup> in their experiments on dogs obtained only concordant curves and the majority of Lewis' tracings were also of this type. When all of these are analyzed, it is found that in Lead I the chief initial deflection was downwardly directed when the right division was cut, and in the opposite direction on transection of the left division. Our results differed from these in that at least half of the curves were of the discordant type. However, when Lead I alone was considered, they were grossly similar to the above. It is a significant fact that in all of our curves, both concordant and discordant, the deflections which were most definitely of the type resembling those seen in humans were found in Lead I. Any deflections which did not correspond exactly to human curves (possibly due to a small part of the division not having been cut) were present in Lead III. Even in our concordant curves, except in one instance, the chief deflection was always less in Lead III than in Lead I, revealing a tendency toward the discordant type. Thus it seems that in deciding on the division which has been affected Lead I is the important lead to study.

Since we have no evidence at present to indicate that the architecture of the junctional tissue, the interventricular septal angle, the position of the heart relative to the standard limb leads or other anatomical factors in the cat more closely resemble the human arrangement than in the dog, we realize that our results cannot be considered completely decisive with regard to the interpretation of human curves.

#### SUMMARY

1. Experiments were performed on cats in which either the right or left division of the bundle of His was cut.

2. Both concordant and discordant curves were obtained. On transecting the right division, the chief initial deflection in Lead I was downward in both types, but in Lead III it was upward in the discordant type and the reverse in the concordant. On cutting the left division exactly opposite results were found.

3. In analyzing the curves, the important lead to study in order to decide upon the location of the lesion appeared to be Lead I.

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## AN ANALYSIS OF THE QRS COMPLEX OF THE ELECTROCARDIOGRAM\*

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CONSIDERABLE evidence has accumulated which indicates that the electrocardiogram, previously interpreted as showing right bundle-branch block, probably is associated with a disturbance of conduction in the left bundle branch. This has cast some doubt upon the applicability of Einthoven's mathematical principles to the abnormal ventricular complexes. It is the purpose of this analysis to demonstrate their applicability as well as their value in understanding the form of the complexes observed in ventricular preponderance, bundle-branch block, and ventricular extrasystoles.

There are certain limitations that must be borne in mind in using Einthoven's method for the study of electrocardiograms. The conditions necessary for calculating the electrical axis by means of the equilateral triangle are approached only when the electrodes are situated in radially different directions and at a sufficient distance from the heart so that all points in the vicinity of each electrode are practically equipotential. (From the standpoint of potential distribution in a fluid-conducting medium, each electrode may then be considered at an almost infinite distance and therefore equidistant from the source.) Wilson and Herrmann<sup>1, 2</sup> have shown that beyond 15 inches from the heart, there is very little potential difference between any two points along the same radial line. Accordingly, this method may be applied to records obtained from the usual limb electrodes but not to records taken with chest electrodes which are less than 15 inches from the center of the heart. With limb electrodes, only the potential differences generated along the frontal plane of the three electrodes are recorded in the standard leads. Consequently, any part of the heart which generates potential differences perpendicular to this plane does not influence the electrocardiogram.

It is well known that the equilateral triangle and the electrical axes calculated from it are merely a schematic approximation of the electrical phenomena actually present in the heart and surrounding tissues. This was stressed by Einthoven<sup>3</sup> who noted, however, that there was sufficient correspondence for practical purposes. Slight variations in the inclination of the axis cannot therefore be used for estimating changes in the direction of the electrical current produced in the heart.

The wave of excitation probably consists of an advancing doublet of positive charges immediately followed by negative charges. This has

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recently been confirmed experimentally by Craib<sup>4</sup> who also disproved the mass theory which hypothesized that relative negativity alone was developed during the excitatory process. Accordingly, the electrical energy generated by an individual muscle fiber is a consequence of the potential difference created by this doublet. The electrical axis at any particular interval represents the direction and is proportional to the magnitude of a potential difference which is the resultant of an algebraic summation of all the individual potential differences produced by activation in the heart at that time. The axis therefore indicates the predominant direction of activation which usually corresponds to the direction of activation in that sector of the heart generating the greatest potential differences at that moment. Craib stated that there could be no quantitative relation between the voltage of the electrocardiogram and the weight of the myocardium in the sense that one is directly proportional to the other. This follows if an increase in weight of the muscle mass is so proportioned that the increments of the various sectors balance each other. If, however, the increase in weight is localized to a sector in which the excitation wave courses in the same general direction, the voltage is affected. When the fibers transmitting the excitation wave longitudinally are thicker in such a sector, the potential differences generated there become proportionately greater and the resultant electrocardiogram is influenced by this alteration.\* If the excitation path is lengthened by increase in length of the individual fibers, the potential differences last for a longer period and consequently alter the electrocardiogram.

In this analysis, the main part of the QRS deflection is considered. The initial part of the QRS complex has been dealt with in another article (Fenichel and Kugell<sup>6</sup>). For purposes of comparison, the axis calculated at the time of the maximum deflections in the three leads is used, as this best represents excitation in the major mass of ventricular musculature. Sometimes the maximum peaks in the three leads do not occur simultaneously but at slightly different intervals. Since all the axes during the period of the maximum deflections usually lie in the same direction, a similar significance may be attached to any one of them.

#### VENTRICULAR PREPONDERANCE

Fig. 1 contains the successive electrical axes of the QRS complexes from a normal electrocardiogram. In constructing the diagram, Lewis's measurements and calculations were used. Each standard lead was taken simultaneously with a direct chest lead so that the precise time

\* The following formula:  $V = \frac{Q}{2\pi kd} \log_e \left( \frac{R_1}{R_2} \right)$  governs the distribution of potential in a thin homogeneous conducting sheet.  $V$  is the potential at any point distant  $R_1$  and  $R_2$ , respectively, from the two poles;  $Q$  is the quantity of electricity flowing in unit time;  $k$  is the coefficient of conductivity of the medium;  $d$  is the thickness of the sheet.

$V$  is in direct proportion to  $Q$  which depends upon the number and thickness of the individual fibers provided they lie in the same direction. Hence the potential difference registered between any two electrodes in the surrounding conducting medium is directly proportional to the mass of these fibers.



relations were known. At 0.0400 sec. the maximum deflections occur in all three leads. The electrical axis at this time is at  $55^\circ$  and is directed downward and to the left.

Fig. 2 is plotted from Lewis' electrocardiogram of left ventricular preponderance which was obtained from a case of chronic nephritis with marked left ventricular hypertrophy. The most prominent initial ventricular deflection is upward in Lead I and downward in Lead III. The

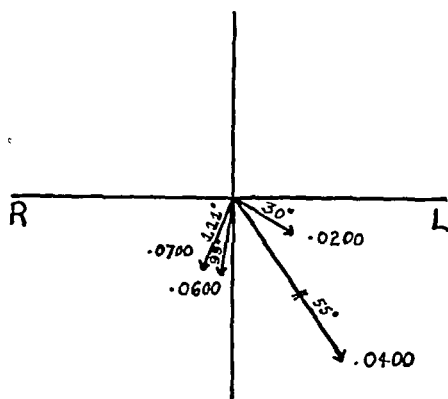


FIG. 1.

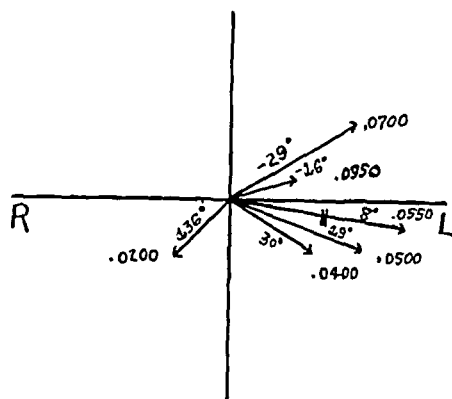


FIG. 2.

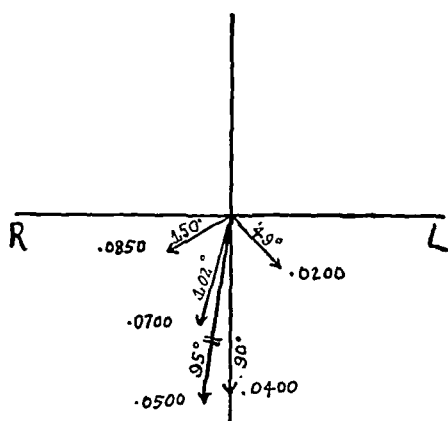


FIG. 3.

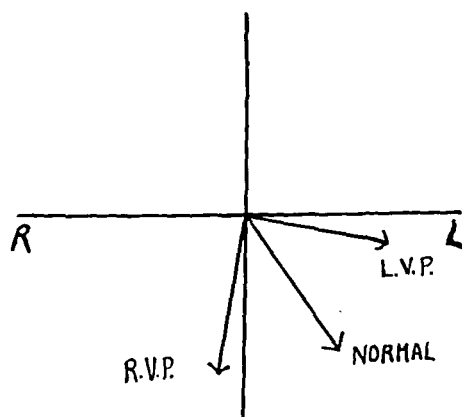


FIG. 4.

Fig. 1.—The electrical axes of successive intervals during the QRS deflections of a normal electrocardiogram. Measurements and calculations from Lewis.<sup>5</sup> The measurements at 0.0400 sec., the time of the maximum deflections, are 6, 11, and 5 for Leads I, II, and III, respectively (in one-fifth millivolts). The length of each axis is drawn somewhat proportional to the manifest potential difference. The axis at the time of maximum deflection is designated by the transverse parallel lines.

Fig. 2.—The axes of a left ventricular preponderance record. From Lewis. Values at time of maximum deflection are 11, 7, and -4.

Fig. 3.—The axes of a right ventricular preponderance record. From Lewis. Values at time of maximum deflection are -1, 9.5, and 10.5.

Fig. 4.—Comparison of the electrical axes of maximum deflection from the previous three figures.

maximum deflection occurs at 0.0550 sec. and the electrical axis is at  $8^\circ$ , pointing almost directly toward the left. During successive intervals, a gradual upward rotation of the electrical axes is evident. This is probably due to the influence of the upward inclining potential differences from the later activated basal portions.

Fig. 3 presents the axes from Lewis' record of right ventricular preponderance observed in a case of mitral stenosis with marked right ventricular hypertrophy. The principal initial deflection is downward in Lead I and upward in Lead III. Here, the maximum of the initial deflection is at 0.0500 sec. and its electrical axis is at  $95^{\circ}$ , downward and slightly to the right.

In Fig. 4 are contrasted the electrical axes at the time of maximum deflection for the three cases given above. The axis for the left ventricular preponderance has rotated to the left of the normal position, while the axis for the right ventricular preponderance has rotated to the right. The rotation of the axis in either case is probably due to the electrical predominance of the wall of the hypertrophied chamber, where potential differences of greater magnitude and longer duration are produced by the activation of the widened and elongated muscle fibers.

The QRS interval in an electrocardiogram showing left ventricular preponderance is often found to be widened to as much as 0.12 sec. This is probably dependent upon the additional time necessary for activating the thicker walls of the hypertrophied chamber. The alteration in the conduction system as a result of dilatation of the chamber may also be a factor in the delay.

For general usage in the interpretation of electrocardiograms, the term axis deviation is preferable to ventricular preponderance, since records resembling those of the latter are obtained from normal individuals without any evidence of ventricular hypertrophy. In such instances, the axis deviation is probably due to the variation in anatomical relations of the ventricles. Left axis deviation records are often observed in sthenic individuals with broad horizontal hearts, while right axis deviation records are seen in asthenic individuals with long vertical hearts.

#### BUNDLE-BRANCH BLOCKS IN DOGS

In the normal electrocardiogram of a dog Wilson and Herrmann<sup>7</sup> observed a QRS interval of 0.043 sec. On cutting the right bundle branch in this dog the interval was increased to 0.067 sec. The difference of 0.024 sec. may then be regarded as the time lost in the aberrant course of the excitation wave traveling through the septum from the left side to the right Purkinje network. These observers then recorded normal ventricular complexes from the same animal by means of properly timed stimuli to the conus region of the right ventricle. A delay of 0.03 seconds or more in the stimulation of the right ventricle resulted in complexes of right bundle-branch block, while less delay yielded complexes which were transitional between normal and right bundle-branch block. It is therefore evident that during the registration of the right bundle-branch complexes, diffuse muscular excitation in the right ventricle began about

0.03 sec. later than in the left ventricle. Moreover, since the normal activation of both ventricles required only 0.043 sec., electrical activity in the intact left ventricle was practically completed at 0.04 sec. and entirely over at 0.05 sec., at which periods the maximum deflections of the aberrant complexes were recorded. Thus it is seen that the maximum deflections of the right bundle-branch complexes represented principally the potential differences of the delayed right ventricular activation which was no longer opposed by the normal left ventricular activation.

The initial ventricular deflections are observed to be higher after section of either bundle branch. This is probably an effect of the unneutralized potential differences produced by the ventricle with the damaged bundle branch. There is no basis for assuming the alternative, that a larger total of potential differences is generated by such a heart. In the transitional complexes of less width, mentioned above, the deflections are not as prominent, since there is less disturbance of the normal balance.

On cutting the right bundle branch in dogs, Lewis, and also Wilson and Herrmann,<sup>7</sup> rather consistently obtained concordant records with the most pronounced part of the initial ventricular deflection negative in the three leads. Wilson and Herrmann later cut the remaining left branch and secured electrocardiograms of complete heart-block. Both observers autopsied all hearts and confirmed the site of the right bundle-branch incision, so that the accuracy of their work can hardly be questioned. On two occasions when the right bundle branch was clamped, Lewis obtained definitely discordant records with upward initial ventricular deflections in Lead I. In analyzing the levocardio-gram, he utilized the latter records which can hardly be considered ideal for experimental deductions, since the preoperative electrocardiograms showed unusually high R-waves in Lead I.

Fig. 5 is plotted from one of Lewis' concordant electrocardiograms with principal deflections downward in all three leads, recorded after section of the right bundle branch. In the tabulation, Lewis presented the measurements for only part of the QRS interval, to 0.0550 sec. After this time, at which the peaks occur in the three leads, the complexes return to the iso-electric line without ever becoming positive. Therefore, all the electrical axes at later intervals are in the same quadrant, upward and to the right. Hence, the actual values beyond 0.0550 sec. are not necessary for this analysis.

Until about 0.0250 sec., the axis is principally directed downward and to the left (at 0.0200 sec. when the early deflections are most prominent). Probably this is due to activation in the intact left ventricle which, to some extent, is balanced by simultaneous septal excitation. After this, the principal deflection appears, and with it there occurs an abrupt rotation of the electrical axis. At 0.0550 sec., the time of

maximum amplitude, the axis points upward and to the right, indicating prevailing activation in the wall of the right ventricle. This is in accordance with the conclusion already noted: that the maximum amplitude of the aberrant complex represents the unbalanced activation in the delayed chamber. In the dog, the right ventricle lies above as

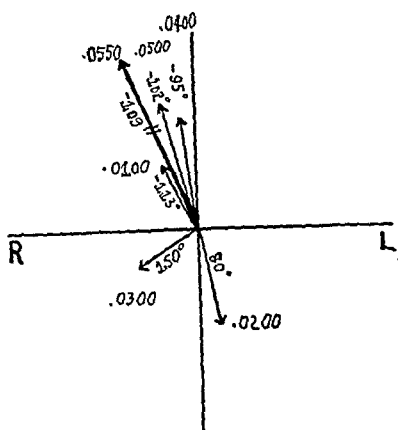


FIG. 5

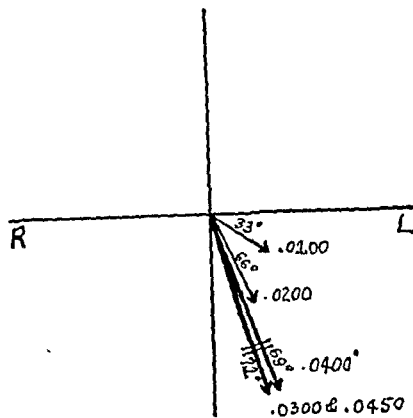


FIG. 6

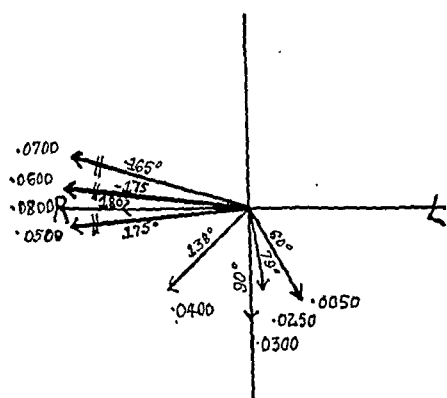


FIG. 7

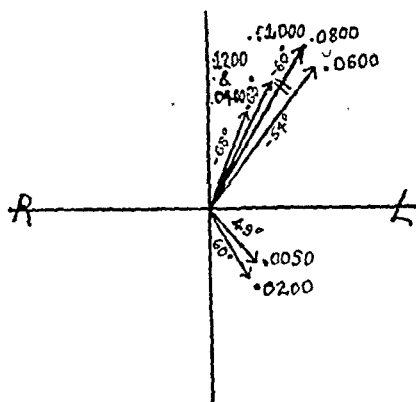


FIG. 8

Fig. 5.—The axes of a record obtained after severing the right bundle-branch in the dog's heart. From Lewis. Values at time of maximum deflection at -5, -15, and -10 (in one-tenth millivolts).

Fig. 6.—The axes of a record following incision of the left bundle-branch in the dog's heart. From Lewis. Values at time of maximum deflection are 4.5, 12.5, and 8.

Fig. 7.—The axes from an electrocardiogram of the infrequent type of bundle-branch block in man. From Lewis. Values at time of maximum deflection are -12.5, -7.5, and 5.

Fig. 8.—The axes from an electrocardiogram of the common type of bundle-branch block (Fig. 10). From a case at Montefiore Hospital. At autopsy, the heart showed marked fibrosis of the entire left side of the interventricular septum. The deflections at successive intervals were measured with a comparator. The values at time of maximum deflection are 11, -11, and -22.

well as to the right of the other ventricle, and its basilar region has more mass than its apical region which rests on the interventricular septum. Thus, the right ventricle in situ resembles an inverted cone. This may account for the marked upward inclination of the axis at the time of maximum deflection, for its direction suggests relative preponderance of the base of that chamber.

The initial ventricular complexes obtained by Lewis, and by Wilson and Herrmann, after cutting the left bundle branch in the dog, are also concordant with the main deflection upward in the three leads. Fig. 6 is charted from one of Lewis' records. Here all the axes are directed downward and to the left. At 0.0400-0.0450 sec., the time of maximum deflection, the preponderant direction of activation is accordingly downward and to the left. Since the dog's left ventricle simulates an upright cone, the direction of these axes can be correlated with the main line of excitation in the left chamber. During the early intervals, the axis is not directed to the right. Septal activation, occurring simultaneously with excitation in the comparatively thin right ventricular musculature, probably overcomes any such tendency.

On inspecting the above two analyses, it is seen that the axis at the time of maximum deflection points in the direction of the chamber

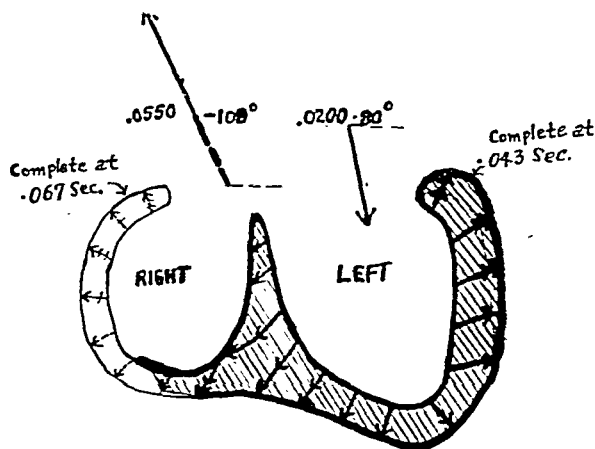


Fig. 9.—Schematic representation of activation in the dog's ventricles after cutting the right bundle-branch. The shaded part indicates the area activated before or at 0.03 sec. The axis at 0.02 sec. conforms to the predominant direction of earlier activation in the left ventricle. The axis at 0.055 sec. corresponds to the predominant direction of later activation in the right ventricle.

whose bundle-branch conduction is impaired, thus representing the activation in the outer wall of that chamber. Moreover, the dextrocardiogram of Lewis (the ventricular complexes observed after severing the left branch) is a representation of activation in the intact right ventricle for approximately only the first third of the QRS interval; and the main part of the complex, which occurs after this, essentially represents the unopposed activation in the wall of the left ventricle. Similar conclusions follow in regard to the levocardiogram. Algebraic summation of the dextrocardiogram and levocardiogram gives a complex resembling the normal complex for only the first third of their intervals or for over half of the normal QRS interval. During this time, the potential differences of relatively normal activation of the right ventricle are added to those of the left ventricle. The slight difference observed between the calculated and the normal complexes is due to the abnormal septal activation. Probably, in bundle-branch block the entire septal wall is activated from the intact side, while in

the normal heart each half of the septum is activated from its own side. To some extent, the potential differences arising from the unidirectional, and consequently slightly prolonged activation of the muscular septum neutralize those resulting from simultaneous activation in the wall of the intact ventricle. This may account for the low voltages recorded during the first third of the QRS interval in records of bundle-branch block.

Lewis recorded the time of arrival of the excitation wave over the surface of the right ventricle in a dog with right bundle-branch block. At 0.0294 sec. after the beginning of the initial ventricular deflection in the simultaneous axial lead, the region of the right ventricle just lateral to the interventricular groove showed activity. The levocardio-gram at 0.0400-0.0550 sec. cannot therefore be considered as representing only left ventricular excitation when there is direct evidence that a part of the right chamber is activated before this time. Fig. 9 is a schematic representation of activation at 0.0300 sec. in the dog's ventricles following severance of the right bundle-branch.

#### BUNDLE-BRANCH BLOCK IN MAN

Before analyzing human electrocardiograms of bundle-branch block, note should be made of some of the essential differences between the human and the canine heart. The left ventricle in man lies posterior to and to the left of the right ventricle. Since the three ordinary leads record only potential differences along the frontal plane, the two ventricles can be regarded as lying lateral to each other. In the frontal plane of the dog, on the other hand, the right ventricle lies above as well as to the right of the other chamber. The QRS interval of the normal complex in man lasts from 0.05 sec. to 0.08 sec., while in bundle-branch block this interval is prolonged from 0.12 sec. to 0.16 sec. As in the dog, the time delay is probably due to the later activation of the ventricle, homolateral to the bundle-branch block. These figures are about double the corresponding measurements in the dog, the human heart being larger and its musculature thicker. Complexes which are transitional between normal and bundle-branch block are also seen in man, and the QRS intervals are accordingly intermediate in duration. Hence, the interpretation of electrocardiograms with left axis deviation, inverted T-wave in Lead I, and normal QRS interval (less than 0.11 sec. which is observed in ventricular preponderance alone) as incomplete bundle-branch block by Lutten and Grove<sup>8</sup> is unwarranted. A normal QRS interval infers simultaneous activation in both chambers.

Fig. 8 is drawn from the measurements of an electrocardiogram (Fig. 10), taken at Montefiore Hospital, showing the common type of bundle-branch block with principal initial ventricular deflection upward in Lead I and downward in Lead III. These curves were not taken simultaneously with a chest lead but were moved until  $e_1 + e_3 = e_2$ . At

autopsy the heart of this patient showed marked fibrosis of the entire left side of the septum. The right side of the septum was intact. At 0.0800 sec., the time of the maximum deflection, the electrical axis points upward and to the left. The axis at maximum deflection in a similar record reported by Lewis, was inclined directly toward the left ( $5^\circ$ ). Since at 0.0800 sec. the normal QRS complex would be either completed or at least beyond the maximum deflection, the excitation in the intact ventricle at this time may be considered almost at an end. Accordingly, at the time of maximum potential, the axis indicates the unbalanced activation of the delayed ventricle. From its

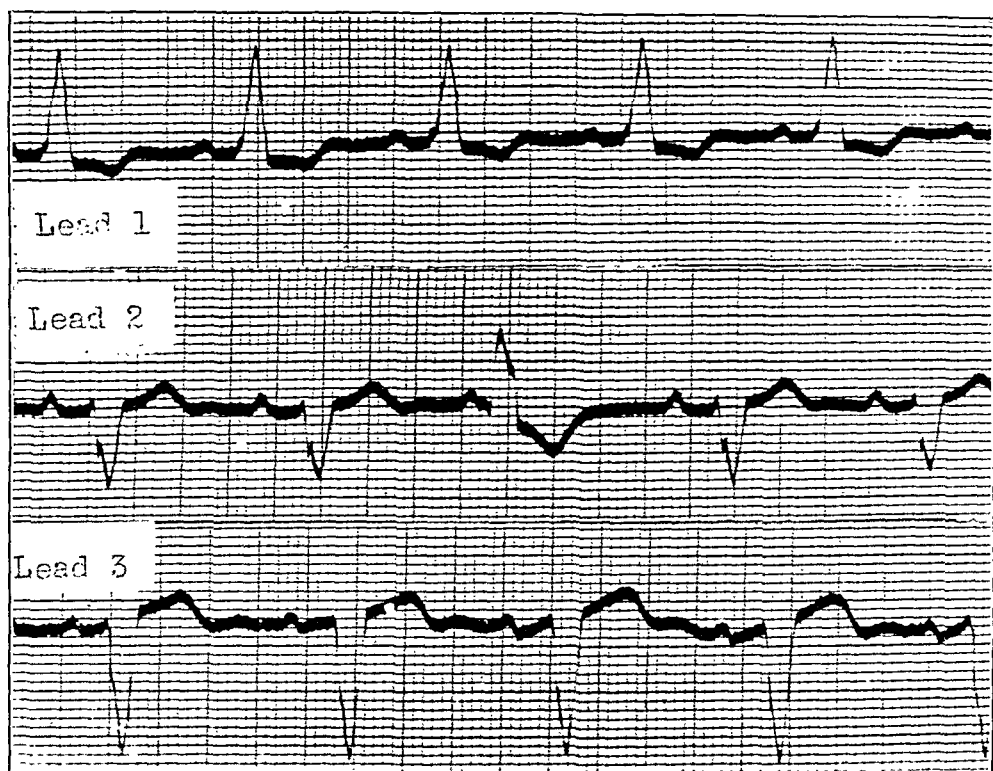


Fig. 10.—The common type of bundle-branch block. QRS interval 0.14 sec. In Lead II, there is a left ventricular extrasystole appearing immediately after the P-wave. This may be explained by the onset of an independent left ventricular excitation process which follows a short time after the normal onset of excitation in the sino-auricular node.

left direction, it can represent only predominant activation in the wall of the left ventricle, and, therefore, the electrocardiogram in question should be interpreted as left bundle-branch block. As in the dog, the axis of maximum deflection points in the direction of the chamber whose bundle branch is blocked. The counterclockwise rotation of the successive axes may be explained by the later activation of the basilar portion of the left ventricle where the excitation wave has an upward inclination.

In his interpretation of a similar electrocardiogram, Lewis considered the axes at early intervals as representing septal activation, and

at later intervals (0.0700 sec.) as representing lateral wall excitation in the intact left ventricle. Therefore, the complex was termed a levocardiogram due to right bundle-branch block. But at 0.0700 sec., as well as until the end of the QRS interval, the axes are still directed to the left. His analysis revealed no evidence of a subsequent activity in the right ventricle, and, therefore, his levocardiogram represented an isolated contraction of the left ventricle. The interpretation presented here explains the activation of both chambers and corresponds to the experimental work in dogs. In 1920 Fahr.<sup>2</sup> from considerations based upon the theory of mass negativity during activation, interpreted the type of record under consideration as left bundle-branch block.

Fig. 7 is plotted from Lewis' electrocardiogram of the less common type of bundle-branch block with principal deflection downward in Lead I and upward in Lead III. At 0.0500-0.0700 sec. the greatest amplitudes occur, and the axes are pointed almost directly toward the right. Their time and direction indicate a later unbalanced right ventricular excitation, and the electrocardiogram should be interpreted as right bundle-branch block. The axis at the time of maximum deflection thus points toward the chamber whose bundle-branch conduction is impaired. In the early intervals, the direction of the axis is probably the result of predominance of left ventricular excitation over aberrant septal activation.

The principal phases of the QRS complexes in the three leads are essentially the same in right bundle-branch block and right ventricular preponderance, since the principal deflections of the former are due to the unopposed potential differences of the retarded right chamber, while in the latter they result from the predominant potential differences of the hypertrophied right chamber. A corresponding similarity is present in regard to left bundle-branch block and left ventricular preponderance. A combination of the two conditions in the same chamber accordingly produces deflections of even greater voltage. The common type of bundle-branch block occurs frequently in patients with hypertension and left ventricular hypertrophy. Hence the complexes are often higher than those of right bundle-branch block records, where concomitant right ventricular hypertrophy is infrequent. Bundle-branch block is differentiated by its wider and notched QRS complexes which are opposite in phase to the T-waves in all three leads. Presumably, the notching is caused by the irregular generation of potential differences on account of delayed activation in one ventricle (Wilson and Herrmann<sup>3</sup>). Displacement of the heart to the left also amplifies the principal deflections of left bundle-branch block. Combinations of right or left bundle-branch block with ventricular preponderance or heart displacement can thus produce many atypical and confusing records with a wide QRS interval. In addition, considerable



pleural or pericardial fluid may reduce the voltage and so distort the record (Oppenheimer and Mann<sup>10</sup>).

#### FUNCTIONAL INTRAVENTRICULAR CONDUCTION DISTURBANCES

Electrocardiograms of bundle-branch block are most frequently seen in cases of coronary artery disease with degenerative changes and fibrosis in the myocardium. A functional impairment in conduction is probably a contributory factor in some cases where no organic lesion is demonstrable in either bundle-branch. With the rapid ventricular rate accompanying auricular fibrillation, the electrocardiogram frequently exhibits such impairment in conduction.

Wolff, Parkinson and White<sup>11</sup> recently reported eleven records of bundle-branch block obtained from healthy young individuals without any evidence of heart disease. The P-R intervals in their tracings are unusually short (often less than 0.1 sec.), so that the wide QRS complexes immediately follow the P-waves without any intervening iso-electric period. Normal complexes preceded by normal P-R intervals were often recorded in this series after release of vagal tone by exercise or atropinization. In the electrocardiogram of one case manifesting an abrupt change from the normal to the abnormal complex, the P-S intervals of both are found to be equal. This means that there is no additional time taken for the entire excitation process from its onset in the sino-auricular node to its completion in the ventricles. Hence, it is suggested that the mechanism is a functional bundle-branch lead rather than block. For some unexplained reason, perhaps vagal influence, there is no retardation at the auriculoventricular node of the auricular impulse to one bundle branch, while the other branch receives its impulse after the normal delay. A left bundle-branch lead would then give ventricular deflections identical with those of right bundle-branch block. Another possibility is that there is present in one ventricle a secondary center which under the influence of the extracardiac nerves stimulates that ventricle at a fixed time after the onset of the sino-auricular impulse. It is interesting to note that Wilson and Herrmann have obtained similar records in dogs on stimulating the right ventricle after cutting the right bundle branch. In one of their records where the direct excitation of the right ventricle preceded the intact left supraventricular activation by 0.031 sec., the wide QRS complexes of complete left bundle-branch block followed immediately after the P-wave. The left ventricular extrasystole in Fig. 10 also resembles the unusual complexes seen in Wolff, Parkinson and White's records.

#### VENTRICULAR EXTRASYSTOLES IN DOGS

It is well known that the complexes of ventricular extrasystoles are similar to those of bundle-branch block. On direct stimulation of either

ventricle, the excitation wave travels through the muscular wall to the endocardium where it spreads rapidly throughout the entire ventricle by means of the Purkinje network. Lewis has shown that a small preliminary deflection results from the passage of the wave through the thick muscular wall, and that the more prominent QRS wave begins with the onset of widespread ventricular activation. The aberrant course of the excitation wave to the second ventricle, probably through the septum, results in retarded and unbalanced activation in that chamber. The resemblance of the complexes of right ventricular extrasystoles and left bundle-branch block can thus be understood.

In 1913, Rothberger and Winterberg<sup>12</sup> studied the form of the complexes obtained on direct electrical stimulation of the dog's ventricles at various points. The electrodes of Lead I were connected to the forelegs. The electrodes of Lead II were placed in a vertical line, one electrode being inserted into the esophagus and the other into the anus. These observers were primarily interested in the form of the ventricular complexes and so did not carefully standardize their electrocardiograms. The normal as well as the extrasystolic complexes were recorded in both leads.

On scrutinizing their recorded extrasystolic complexes, it is seen that the electrical axes of the principal deflections are directed toward the later activated ventricle. A complex with the principal deflection upward in Lead I was obtained upon stimulation at all points on the right ventricle. The positive deflection indicates that all the axes at the time of maximum amplitude point toward the left (Lead I represents the horizontal vector of the electrical axis). On stimulation of the surface of the left ventricle, a complex with a negative principal deflection in Lead I was obtained at all points but three, which are located at the apex near the interventricular sulcus. Thus, all left ventricular axes except those calculated from points on the apex are directed toward the right.

The initial ventricular deflections from the three points at the apex of the left ventricle are found to be of almost normal width when the preliminary deflections, due to the initial passage of the excitation wave through the thick muscle wall, are not included. By direct electrical stimulation at the apex of the left ventricle, Lewis obtained similar intermediate complexes for some distance to the left of the interventricular sulcus. Such complexes also resemble the transitional type which Wilson and Herrmann produced by slightly delayed stimulation of the ventricle with a severed bundle branch. In each instance the type of complex is dependent upon almost simultaneous activation in both ventricles. Accordingly, it can be seen why the axes of the complexes obtained at the apex by Rothberger and Winterberg approximate the normal axis which is directed toward the left (in the dog, the main deflection of the normal QRS complex in Lead I is upward).

Upon stimulation at the left apex, more rapid conduction along the longer path to the right Purkinje network may account for the approximately simultaneous activation of the two ventricles. In his observations on the course of the excitation wave in the auricles, Lewis found the conduction rate to be 1252 mm. per second along the interauricular band, whereas it was only 588 mm. per second near the superior vena cava. This difference in rate, he attributed to the oblique direction of the fibers along the latter path. Therefore, it may be assumed that muscle fibers conduct the excitation wave more rapidly along their long axes. On section of the heart, Lewis observed that the muscle fibers at the left apex coursed laterally toward the right ventricle. Hence, the more rapid conduction of the excitation wave to the right ventricle is prob-

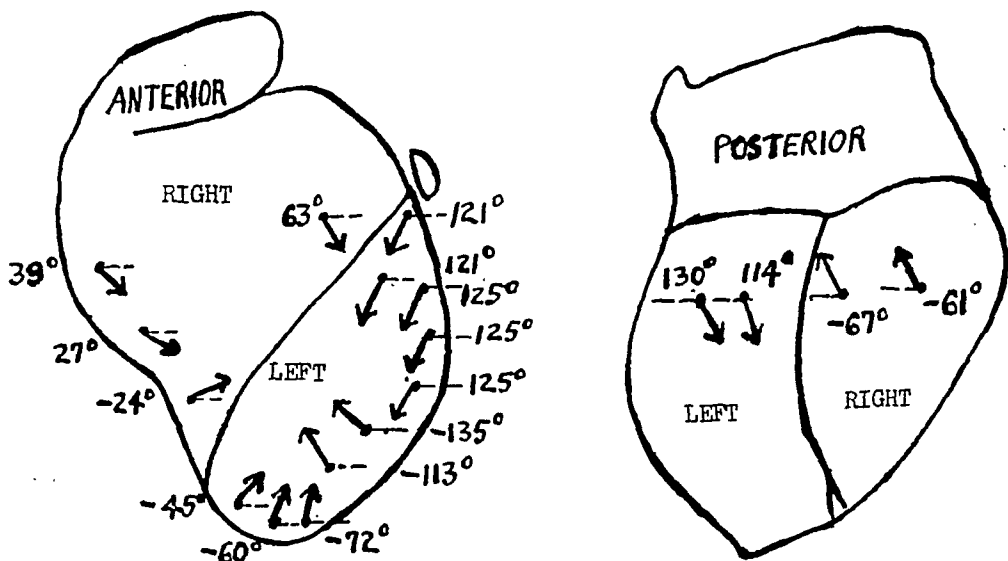


Fig. 11.—Diagrams of the anterior and posterior surfaces of the dog's ventricles with Rothberger and Winterberg's points of stimulation. The axis charted at each point is calculated from the abnormal QRS complexes which they obtained upon stimulation at that point.

ably due to transmission along the length of the fibers, while conduction to the left ventricle occurs across the fibers.

In the experiments of Rothberger and Winterberg, Lead I is practically at right angles to Lead II, and since they represent respectively, the horizontal and vertical projections of the electrical axis, the latter can be calculated. In view of the fact that the ratio of the maximum amplitudes of the normal complexes in both leads is fairly constant, standardization for comparative study is possible. This has been accomplished by correcting the values of the maximum deflections of the extrasystolic complexes in proportion to a fixed ratio of the normal complexes. Because of the use of four different dogs and the presence of overshooting in several records, some margin of error is to be expected. The error is found to be relatively slight in comparison with the marked variation in the complexes recorded at the different points of stimulation.

Diagrams are presented of the anterior and posterior surfaces of the

dog's heart with the points of stimulation (Fig. 11). The axes charted at these points are calculated from the maximum deflections of the abnormal complexes in their records. As noted above, the axes of all points on the surface of the right ventricle point toward the left. Except for the apical region, all left ventricular points show a deviation of their axes toward the right. A regular rotation of the electrical axes is seen from cephalic to caudal points. The axes of the former have a downward direction while those of the latter incline upward. The explanation of the right or left direction is presented in the discussion of bundle-branch block. The rotation of the axes between superior and inferior points of the same ventricle is considered later.

#### EXTRASYSTOLES PRODUCED IN MAN

Barker, Macleod, and Alexander<sup>13</sup> recently obtained electrocardiograms following direct electrical stimulation of the human heart. The subject had streptococcus pericarditis for which the pericardial sac was widely opened after the resection of several ribs. The lower portion of the ventricles being thus exposed, the relations of the points of stimulation could be determined fairly accurately. The ventricular complexes which they obtained resemble those of ventricular extrasystoles and bundle-branch block seen in clinical electrocardiograms. The main initial ventricular deflection is upward in Lead I for all points on the surface of the right ventricle, and downward for all points on the surface of the left ventricle. Hence, the principal deflections in Lead I are in the same phase as those of bundle-branch block of the opposite chamber. A preliminary deflection due to the passage of the excitation wave through the muscle wall is also seen in the complexes from points on the left ventricle.

In Fig. 12 are charted the electrical axes of maximum deflection at the points of origin. Any inaccuracy in measuring the maximum deflections in their records is almost negligible in comparison with the marked variations of the complexes at the different points of stimulation. The axes of all right ventricular points are directed toward the left, while the opposite holds true for points on the surface of the left ventricle. In each instance, the axis is directed toward the later excited chamber.

Barker et al observed prominent variations of the main deflections in Leads II and III between cephalic and caudal points of the same ventricle (points 10, 7, 6, 4). At point 10, the main deflections were upward in Lead II and Lead III, while at point 4 they were downward in the two leads. Since the main deflections in Lead I were upward at both points, the complexes of point 10 were concordant and those of point 4 discordant. They suggested that this probably resulted from the altered order in which various portions of the ventricles became active.

An analysis of the electrical axes yields an explanation for these variations in the complexes. On observing the electrical axes in Fig. 12, a

regular rotation is evident at points along a vertical line. The axes of the superior points of each chamber have a downward direction while those of inferior points have an upward direction. The same observation is noted in the forced ventricular contractions produced by Rothberger and Winterberg in the dog's heart (Fig. 11). During normal activation in either ventricle, the many divisions of the bundle branch distribute the excitation wave rapidly over the entire Purkinje network so that the various regions differ only slightly in the time of arrival of the excitation wave (in proportion to their distance from the bundle branch, the

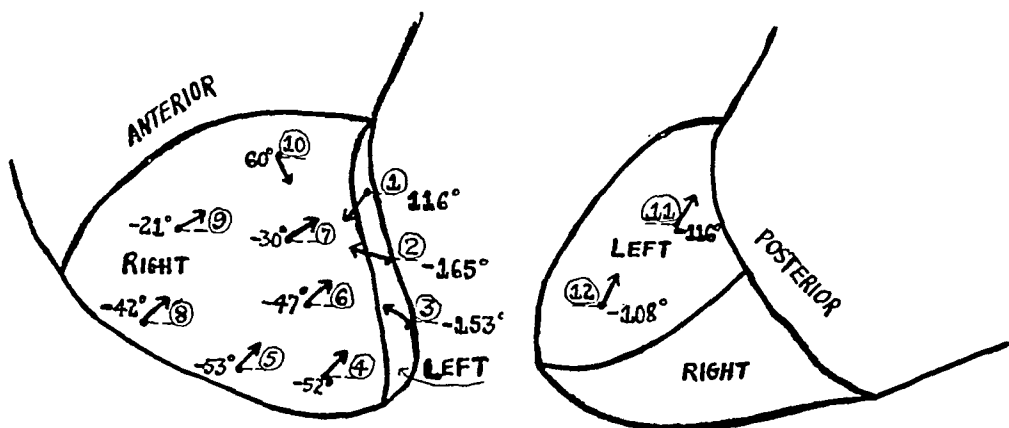


Fig. 12.—Diagrams of the lower anterior and posterior surfaces of the human ventricles showing Barker, Macleod, and Alexander's points of stimulation with the axes calculated from the recorded complexes.

basilar regions receiving the wave somewhat later). When, however, either ventricle is stimulated at a cephalic point, the underlying Purkinje network transmits the excitation wave to the superior half of that ventricle first. Since the lower portion of this ventricle is activated later, part of its excitation remains to oppose the delayed excitation in the other ventricle. Consequently, the downward directed potential differences generated by the lower portion of the first ventricle divert the electrical axis of maximum deflection, resulting essentially from activation in the wall of the second ventricle, somewhat downward. In a similar manner, upon stimulation at a caudal point, the upward inclined potential differences generated in the later excited superior portion of the first ventricle elevate the axis of maximum deflection. Furthermore, the axis of an intermediate point approximates that of a bundle-branch block of the opposite chamber. The axis at point 7 is 30° upward and to the left, whereas the axis of maximum deflection in the record of left bundle-branch block in man, presented above, is 60° upward and to the left. The axis of point 2 is 15° upward and to the right, while the axis in the record of right bundle-branch block is 5° upward and to the right.

In clinical electrocardiograms, it is possible that the exact origin of a ventricular extrasystole may be ascertained after calculating its axis of maximum potential and comparing it with those charted in Fig. 12. In

the experiments of Barker et al, the outer surface of the ventricle was stimulated, whereas ventricular premature beats are thought to arise from foci in the Purkinje tissue. This difference in the origin of the impulse may alter the time at which various regions of the ventricle are activated, so that comparison is not fully justifiable. In addition, other conditions, such as preponderance in one ventricle or position of the heart, affect the direction of any axis and offset calculations. Nevertheless, it is reasonably certain that a premature ventricular contraction originates in the right ventricle, if its main QRS deflection is upward in Lead I, while a main downward deflection in Lead I signifies left ventricular origin.

Wilson, Macleod, and Barker<sup>14</sup> recently demonstrated the inadequacy of Lewis' interpretation of the particular side involved in either type of bundle-branch block and presented a nomenclature similar to the one in this paper. However, in applying the principles of excitation deduced from the hypothetical shell of muscle to the excitatory process in the ventricles, Wilson and his associates disregarded some of Lewis' well-established observations. During normal ventricular activation, they assumed that the entire endocardium as well as the adjacent muscle tissue becomes activated almost simultaneously. Accordingly, the direction of the electrical axis becomes essentially an inverse function of the ventricular breaks or openings where no opposing electromotive force exists. Yet there is sufficient evidence to indicate that the various endocardial regions are not activated simultaneously and that the entire QRS interval is not required for excitation of the muscle walls alone. Lewis and Rothschild's endocardial readings show a very rapid, almost simultaneous, activation in the dog's right ventricle, but this may be due to the special bridge of conducting tissue which extends across the chamber. The endocardial readings in the left ventricle were not considered very reliable because of the disturbing influence of the strong muscular contractions. Nevertheless, the epicardial readings of both ventricles point to a later activation of the bases that cannot be accounted for solely by the thickness of the underlying muscle wall. Although conductivity in the specialized conducting tissue is five to ten times more rapid than in the ordinary myocardium, the path through the former is at least five to ten times longer than that through the thickest part of the ventricular wall. It is therefore more reasonable to infer that the time necessary for the impulse to reach any point of the endocardium is directly proportional to the distance from its bundle branch and that the activation of the nearer muscular regions dominates the early QRS deflections. Hence a correlation of the electrical axis with the particular regions probably activated at that time appears to be a more direct and less complex method of analyzing the excitatory process than the method in which a correlation with the ventricular openings is sought. In accordance with Lewis' concept, the QRS interval can readily be divided into an early

period, approximately the first third representing excitation principally in the septum and adjacent inferior portions of both ventricles, and a later period containing the maximum deflection and representing lateral wall and basal excitation. A division into shorter periods is impracticable because of considerable overlapping in the time of activation of different sectors.

The form of the canine electrocardiogram is definitely altered by cutting the anterior or posterior division of the left bundle branch while the QRS interval remains unaffected. This would favor the view that a disturbance of the normal order of activation has occurred in that chamber, i.e., the activation of the region previously supplied by the incised division becomes somewhat delayed, although its excitation still occurs before the process is completed at the base. It is difficult to account for such an alteration merely by a modification in the tangential components which may be accurately applicable to the hypothetical shell of muscle but not to the heart, where several distorting factors are present. While the tangential components dominate the electrical effects produced by the endocardial network, the voltage from this source is too small to be recorded in the electrocardiogram. Even with a complete reversal of the direction of the excitation wave in the endocardial network, the influence of the tangential components upon the path in the muscle tissue is quite small, inclining the line of excitation only  $11^{\circ}$  to  $23^{\circ}$  from the normal line (2a where  $\tan a = 1/10$  to  $1/5$ ). Moreover any tendency of varying tangential components to divert the excitation wave from the usual path is offset by the fixed position of the individual muscle fibers in relation to the endocardial network from which the impulse is received, and by the constant conduction of the excitation wave along the length of the individual fibers, since longitudinal transmission is probably more rapid.

Wilson, Macleod, and Barker maintained that the prominent deflections of the QRS complexes in bundle-branch block are primarily due to the aberrant activation of the entire septum from the intact side, and they therefore stressed the importance of the position of the septum. But we have sufficient data available to believe that the septum is activated fairly early, and this appears likely since the septum is nearest to the intact bundle branch. Subsequent to severance of the right bundle branch, right ventricular activity just beyond the intraventricular groove was detected at 0.0294 sec. by Lewis and Rothschild whereas the maximum deflection of the abnormal complex usually occurs later (about 0.04-0.055 sec. in the dog). Wilson and his coworkers' statement that the later and major part of the canine dextrocardiogram may be attributed to the electrical effects of activation of the septum and right apical region is open to the criticism that time relations were not considered, for Lewis and Rothschild showed that in the intact heart the outer surface of the right apex usually becomes active at 0.0120 sec.

According to Wilson, Macleod, and Barker, the major deflections recorded in hypertrophy of one ventricle may be a consequence of the augmented electrical effects of the opposite half of the hypertrophied septum. Although the septum is hypertrophied, the effects of activation entering from one side tend to neutralize those of simultaneous activation from the other side. The concept advanced in this paper is similar to their alternative view, that the axis deviation may be due to increased electrical effects from the wall of the hypertrophied ventricle. The preliminary deflections in ventricular preponderance are correlated with septal position in a previous communication (Fenichel and Kugell). There is at present no basis for assuming that they are sequential to some delayed activation in the hypertrophied chamber.

#### SUMMARY

1. In ventricular preponderance, the deviation of the electrical axis is probably an effect of the greater potential differences generated by the wall of the more hypertrophied ventricle.

2. The principal initial ventricular deflections of bundle-branch block represent the unopposed potential differences of delayed activation in the wall of the ventricle with impaired conduction.

3. The principal deflections of ventricular extrasystoles result from the unopposed potential differences of delayed activation in the ventricle, contralateral to the one from which the excitation impulse arises.

*Note at time of correction of proof:* The recent experimental studies of bundle-branch block in the cat by Roberts, Crawford, Abramson and Cardwell<sup>15</sup> are also contrary to the former interpretation of bundle-branch block. In Lead I they obtained a negative principal deflection after incision of the right bundle branch and a positive principal deflection after incision of the left bundle branch.

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## Department of Clinical Reports

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### CHANGES IN THE ELECTROCARDIOGRAM IN THE COURSE OF PERICARDIAL EFFUSION WITH PARACENTESIS AND PERICARDIOTOMY\*†

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**E**LECTROCARDIOGRAMS obtained soon after coronary occlusion have so regularly shown the R- or S-T segments originating on the terminal limb of R or S before the latter reaches the iso-electric level, that such findings have been considered almost pathognomonic of acute coronary closure.

In the experimental animal such R- or S-T abnormalities have been observed after coronary ligation,<sup>1, 2</sup> after injection of toxic material into the muscle of the ventricle,<sup>3</sup> after a toxic dose of digitalis,<sup>4</sup> after injection of fluid into the pericardium,<sup>5</sup> and during induced general anoxemia.<sup>6</sup>

That such "plateau type" R-T segments may occur in clinical conditions other than coronary occlusion was first shown by Scott, Feil and Katz,<sup>7</sup> who in 1929 reported this finding in a case of aneurism ruptured into the pericardium and in a case of purulent pericardial effusion. In neither instance was coronary disease found at autopsy. These authors attributed the electrocardiographic changes to increased hydrostatic pressure in the pericardial sac which, in their opinion, caused anoxemia of the heart muscle. Shearer,<sup>8</sup> and later Master and his associates<sup>9</sup> reported the occurrence of this abnormality of the electrocardiogram in the course of lobar pneumonia with a subsequent return to normal in the patients who recovered.

We have had the opportunity to observe a patient with pneumococcal pericarditis with effusion, in the course of which paracentesis and later pericardiotomy were done, in whom daily electrocardiograms showed the "plateau type" of the R-T segment returning to normal in the presence of severe toxemia, progressing to death on the twenty-first day. No coronary disease nor gross myocardial damage was found at autopsy.

#### CASE REPORT

A white male, aged thirty-five years, was admitted on December 26, 1930, in severe shock complaining of pain in the left side of the chest and of prostration. He had been under our observation for two weeks with cough and fever ranging from 99° to 103° F. Physical signs during this time were negative except for inflammation

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of the upper air passages. This seemed to be subsiding until the day before admission when he was suddenly seized with intense pain in the precordia that required morphine for relief. On admission there was shock, with rapid shallow respiration and also marked cyanosis. The blood pressure could not be satisfactorily determined. The left border of the heart was about 12 cm. from mid-sternum, no arrhythmia was present and no murmurs or pericardial frictions were heard. Dullness was present over the left lung base, and a harsh pleural friction was heard in the precordial area. After a roentgenogram had showed the heart shadow greatly enlarged, a diag-

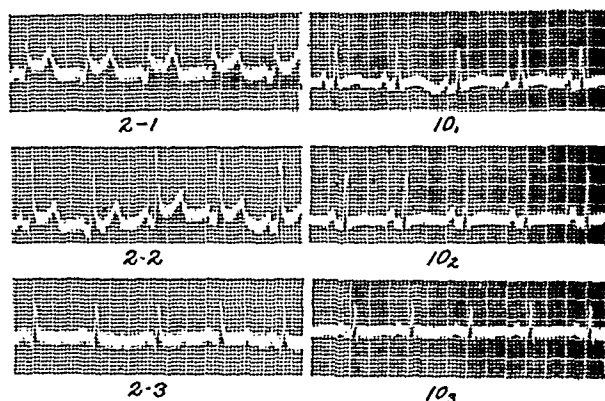


Fig. 1.—(Left) Record taken on the third day of illness showing elevation of the R-T segment in first and second lead. (Right) Record taken on eleventh day of illness showing normal R-T segments.

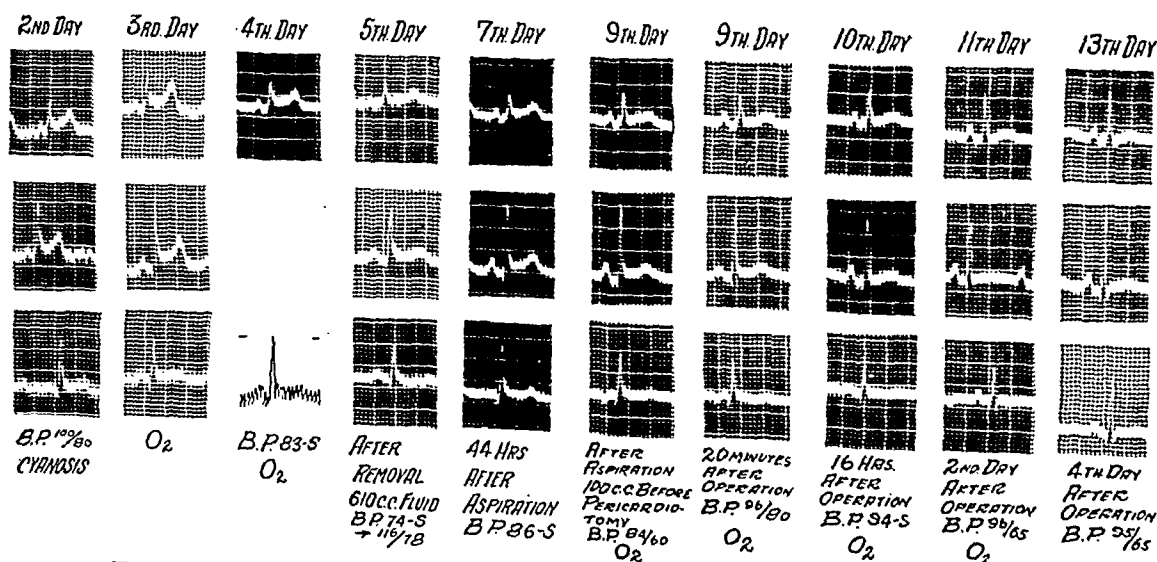


Fig. 2.—Single complexes from the three leads of records obtained during the clinical course. These with the clinical notes below each record show the lack of change during the administration of oxygen, and the gradual return to normal following removal of fluid.

nosis of acute pericarditis with effusion was made. On the following day a to-and-fro friction was heard over the precordia. The first electrocardiogram, which was made on December 27, suggested that we might be dealing with coronary occlusion rather than with pericardial effusion, and the original diagnosis might have been relinquished but for the physical signs and roentgenograms typical of pericardial effusion and for the observations of Scott, Feil and Katz previously referred to. On account of marked cyanosis, anoxemia was presumed to be considerable and oxygen was administered continuously at the rate of 5 to 6 liters per minute. This was followed by definite decrease in the cyanosis, though the character of the electrocardiogram was unaltered.

The blood pressure showed a progressive fall; on December 27, 100 systolic, 80 diastolic; on December 29, 83 systolic and on December 30, 74 systolic. Paracentesis was done on December 30, and 610 c.c. of slightly turbid fluid were removed. Following paracentesis the blood pressure rose to 116 systolic and 78 diastolic. On January 3, 1931, 100 c.c. of pus were aspirated and pericardiotomy was advised and was done on the same day.

At operation about 150 c.c. of pus under slight pressure were evacuated. Oxygen, which had been discontinued following the paracentesis, was readministered. Transfusions of 250 to 300 c.c. of blood were given on January 6, 8, and 10 in an effort to combat the toxemia, which seemed the dominant factor in the illness. Later, when blood cultures showed a growth of *Pneumococcus* Type I, antipneumococcic serum (Felton) was given. Death occurred on January 15, 1931, apparently from toxemia which had progressed steadily from the onset.

#### DISCUSSION

Changes in the R-T segment of the electrocardiogram such as are present in this case have been attributed to a number of factors among which are: (a) injury to the ventricular muscle, (b) toxemia, (c) general anoxemia, and (d) anoxemia of the heart muscle. In the case here reported three of these conditions were present and must be considered as possible factors.

Toxemia, to which such changes in the electrocardiogram occurring in pneumonia, have been attributed by Master and his associates,<sup>9</sup> was present and progressive, and in our opinion was the cause of death. It is interesting to note that the infection was caused by the *Pneumococcus* Type I. Since normal electrocardiograms were obtained at a time when the toxemia was the dominant feature of the illness, we believe that it was not a considerable factor in this case.

In considering the rôle of general anoxemia, we have no determinations of the oxygen content of the blood, but have assumed that the presence of marked cyanosis and rapid shallow respirations, which were relieved following the administration of oxygen, was indicative that anoxemia was present to a considerable degree. The electrocardiograms taken while oxygen was being given were similar in every respect to the ones obtained previously, so that it seems fair to conclude that general anoxemia was not the dominant factor in the production of the electrocardiographic changes.

The first change toward normal in the electrocardiogram was noted in the record taken immediately after removal of 610 c.c. of fluid by paracentesis on December 30 and consisted of slight but definite lowering of the R-T segment and diminished amplitude of the T-wave. It may be assumed that the hydrostatic pressure within the pericardium continued to be less after this paracentesis, since only 100 c.c. of pus were obtained by aspiration on January 3 and only 150 c.c. found on pericardiotomy on the same day. This fall in pressure was paralleled by gradual return of the electrocardiogram to normal, which point was reached on January 5.

These clinical observations together with daily electrocardiograms seem to us to confirm the conclusions of Scott, Feil and Katz, that the electrocardiographic abnormalities resulted from local anoxemia of the heart muscle arising from the tamponade effect of increased hydrostatic pressure within the pericardium.

#### CONCLUSIONS

We believe that increased hydrostatic pressure within the pericardium, diminishing both venous return and coronary flow, resulting in anoxemia of the heart muscle, was the dominant factor in the electrocardiographic abnormalities in this case.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Lichtman, S. S.: Isolated Congenital Dextrocardia. Report of Two Cases With Unusual Electrocardiographic Findings: Anatomic, Clinical, Roentgenologic and Electrocardiographic Studies of the Cases Reported in the Literature. *Arch. Int. Med.* 48: 683, 1931.

Isolated dextrocardia is defined in its strictest sense as a primary independent dextroposition of the heart. In this article a clinical analysis of the symptoms, signs, roentgenographic and electrocardiographic evidence and diagnostic features is attempted, based on a study of one hundred and sixty-one cases of isolated dextrocardia reported in the literature.

Etiologic, pathogenic and anatomic considerations are reviewed. A comprehensive classification inclusive of known and possible anatomic variations is presented.

Two personal cases are presented with unusual electrocardiographic findings, the result of associated congenital cardiac malformations and their effects.

Carter, Edward P., and McEachern, Donald: Recurrent Complete Heart Block. Report of a Case Associated With Transient Bundle-Branch Block and Normal Conduction Between Attacks. *Bull. Johns Hopkins Hosp.* 49: 337, 1931.

The patient whose illness is reported illustrated a number of unusual and interesting points with regard to the cardiac mechanism and its reaction to various drugs. Briefly these were: (1) recurrent complete auriculoventricular dissociation (and Adams-Stokes seizures) with normal conduction between attacks; (2) paroxysmal bundle-branch block; (3) an idioventricular rhythm, during the periods of complete auriculoventricular dissociation, which arose sometimes on the left side and sometimes on the right; (4) the development of ventricular tachycardia following an overdose of epinephrine intravenously; (5) the onset of status anginosus during thyroid therapy.

The details of these observations are reported together with a possible explanation for their occurrence.

MacCallum, W. G., and Taylor, J. Spottiswood: The Typical Position of Myocardial Scars Following Coronary Obstruction. *Bull. Johns Hopkins Hosp.* 49: 356, 1931.

The importance of recognizing the scarred area in the heart following obstruction of a coronary artery slowly produced by arteriosclerosis and often completed by thrombus formation is pointed out. There is a gradual wasting of the cardiac muscle in the affected area somewhat smaller than that ordinarily supplied by the obstructed artery with replacement by fibrous tissue.

Three typical photographs from a long series of specimens are reproduced to show the contrast between the effect of obstruction of the anterior descending branch of the left coronary artery, of its left circumflex branch and of the right coronary artery.

Weinstein, Alfred A., and Weiss, Soma: The Significance of the Potassium-Calcium Ratio and of the Inorganic Phosphorus and Cholesterol of the Blood Serum in Arterial Hypertension. *Arch. Int. Med.* 48: 478, 1931.

A study of the significance of the potassium calcium ratio and the inorganic phosphorus and cholesterol of the blood serum in seventy-five cases of hypertension and twenty-five control cases is presented. This investigation was undertaken to determine whether or not changes could be demonstrated in the level of the potassium calcium and cholesterol of the blood tested by the reliable methods available and when the patients were selected after a detailed investigation of the clinical state. Since the calcium level of the blood varies inversely with the inorganic phosphorus level, determinations of the inorganic phosphorus were also performed.

The average potassium level rose from 20 to 22.15 mg. per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without secondary complications. This rise was most marked in cases of hypertension with cardiac involvement in which the average level was 22.8 mg. per hundred cubic centimeters. The average calcium level in these cases was normal (9.75 mg. per hundred cubic centimeters) as compared with that of the control group (9.8 mg. per hundred cubic centimeters).

The correctness of the observations on the normal amount of calcium in arterial hypertension was supported by the fact that the inorganic phosphorus level in these cases (4.1 mg. per hundred cubic centimeters) showed no tendency to increase above the average amount of inorganic phosphorus in the controls (4.3 mg. per cent) while the calcium inorganic phosphorus ratio of the seventy-five cases of hypertension (2.43) showed no tendency to fall below that of the control cases (2.33). The potassium calcium ratio rose from a control level of 2.05 in twenty-five cases to 2.32 in seventy-five cases of hypertension with or without involvement. This rise was most marked in patients with hypertension and cardiac involvement (2.38) and least in patients with uninvolved hypertension (2.19). The slight increase observed in the cases of hypertension was probably due to the impairment of the circulatory functions.

The cholesterol level rose from a control level of 171.6 to 204.5 mg. per hundred cubic centimeters in seventy-five cases of hypertension with or without involvement. This was most marked in patients with hypertension and renal involvement (227 mg. per hundred cubic centimeters) and least in patients with hypertension and cardiac involvement (194 mg. per hundred cubic centimeters). Of thirty-seven cases of uninvolved hypertension, only five (13 mg. per hundred cubic centimeters) showed an unexplainable hypercholesteremia. There was no relation between the potassium ratio and the cholesterol content of the blood in hypertension.

Neither changes in the potassium calcium ratio nor changes in hypercholesteremia can be considered as playing a fundamental rôle in the development of arterial hypertension. Elevation of the potassium and cholesterol levels observed in one group of patients with hypertension is the result rather than the cause of changes in the cardiovascular system in arterial hypertension.

Harrison, T. R., Turley, F. C., Jones, Edgar, and Calhoun, J. Alfred: Congestive Heart Failure. X. The Measurement of Ventilation as a Test of Cardiac Function. *Arch. Int. Med.* 48: 377, 1931.

A series of standard exercises has been described during and after which the ventilation was measured. The expression:

$$\frac{\text{ventilation}}{\text{vital capacity}} \times \frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2}$$

been denoted as the ventilation index, and the values for this are relatively independent of the nutritional state. It is believed that the ventilation index affords a fairly accurate objective answer to the question of breathlessness.

From the data obtained during the study it is felt that dyspnea is directly proportional to the ventilation per square meter and inversely proportional to vital capacity. The degree of dyspnea is closely proportional to the expression:

$$\frac{\text{ventilation}}{\text{vital capacity}}$$
 It was found that the actual dyspnea was greater in obese subjects and often less in very thin subjects than in persons of normal nutritional status. It was also found that the index was usually normal in subjects with cardiac neurosis. The ventilation index was found to be usually slightly above normal in subjects with early organic cardiac disease and was very much above normal in patients who have or who have had congestive failure. The ventilation index was also increased in persons with diminished vital capacities from pulmonary disease, in subjects with hyperthyroidism and in patients with severe anemia. The test is useless and actually misleading in persons with respiratory obstruction.

The authors believe that the test will be of some value in measuring the effect of various therapeutic measures, such as the administration of digitalis in patients with different types of cardiac disease in various stages of development.

Priestley, James T., Markowitz, J., and Mann, Frank C.: The Tachycardia of Experimental Hyperthyroidism. *Am. J. Physiol.* 98: 357, 1931.

A series of experiments was performed by which it was shown that the heart rate of perfused hearts of thyroxinized rabbits and the heart-lung preparation of thyroxinized dogs is considerably greater than normal. Similarly, when the heart of a small dog is transplanted into the neck of a large dog by means of anastomosis of blood vessels, the administration of thyroxin evokes definite tachycardia of the transplanted heart. It appears that the tachycardia of experimental hyperthyroidism is not dependent on the central nervous system but on a peripheral mechanism.

Brams, W. A., and Katz, L. N.: Studies on the Overdistended Heart. I. Effects of Venesection. *Am. J. Physiol.* 98: 556, 1931.

The effects of venesection on the nondistended and on the previously acutely, overdistended heart of the anesthetized dog were compared. The overdistention was brought about by transfusion of defibrinated blood, physiological saline, gum acacia solution or by a mixture of the former two. The analysis was based on a study of graphically recorded volume curves, on optically recorded synchronous pressure pulses from the two ventricles, and from the aorta and pulmonary artery, on the pressure levels in the systematic and pulmonary veins, and on the electrocardiogram recorded by the three standard indirect leads.

Venesection in the nondistended heart caused a reduction in stroke volume of the ventricles, a decrease in the maximum pressure and pressure excursion of the ventricles during systole and a fall in the pressure level in the aorta and pulmonary artery. These changes are in accord with previous work on the effect of hemorrhage. The changes were more marked in the left ventricle and aorta. The stability of the diastolic pressure in the pulmonary artery was striking.

The subsequent course of events, which was followed for twenty minutes, was variable. In some experiments there was a progressive decrease in the pressure and stroke volume; in others there was a tendency for the pressure and stroke volume to increase again; in a few there seemed to be a stabilization of the heart's activity at the new level.

Venesection produced a different set of events in the acutely overdistended heart. In many instances venesection led to a further drop in stroke volume of the ventricles, a further decline in the maximum pressure and the pressure excursion of the ventricles during systole, and a further fall in the pressure level and pulse pressure in the aorta and pulmonary artery. In every one of the experiments in which this initial depression of the heart's action was noted, a further progressive depression was observed in the following periods up to twenty minutes. No instance of a secondary augmentation of the pressure levels or excursions was noted, probably because of the escape of the fluid (whose osmotic pressure was low) from the blood stream. The changes were more marked in the left ventricle but, unlike the nondistended heart, venesection produced, as a rule, a greater drop in the diastolic pressure of the pulmonary artery than in the aorta.

In some experiments venesection overcame the depressing action of overdistention, leading to a temporary or lasting improvement, at least up to twenty minutes. This improvement was evidenced by an augmentation of the stroke volume, by an elevation of the maximum pressure and pressure excursion of the ventricles during systole or both, and by a rise in the systolic and pulse pressures in the aorta and pulmonary artery, occasionally accompanied by a rise in the diastolic pressure level and by a fall in the pressures in the systemic and pulmonary veins.

Venesection in the previously overdistended heart was always associated with a decrease in diastolic volume and in initial pressure, the drop in the latter being as a rule greater in the left ventricle. In the nondistended heart, bizarre variable changes were noted in the initial pressure, although the diastolic volume consistently dropped. These bizarre changes in initial pressure are ascribed to artefacts inherent in the experimental method which are sufficiently large to mask occasionally the true changes in the nondistended heart but not the larger changes in initial pressure following venesection in the overdistended heart.

The results reported indicate that venesection has a different dynamic effect on the acutely overdistended heart than on the nondistended one. In many instances an improvement in the dynamic action of the overdistended heart can be demonstrated; in others, however, the depression of the overdistended heart's pumping ability is apparently made progressively worse by venesection.

It is realized that the acutely overdistended heart in these experiments is not strictly comparable with the overdistended heart encountered clinically and that such factors as the presence of myocardial pathology and chronicity of the stasis and its effects, may alter the response to venesection. With these reservations, it is believed that considerable information has been gained in these experiments which may lead to a better evaluation of the clinical possibilities of venesection.

The changes in heart rate following venesection were variable in both the nondistended and the overdistended heart. The effect of these rate changes on the dynamics of the heart was evaluated in making the analysis of the results of venesection. Temporary or permanent slowing was as frequent a finding as acceleration. Slowing was usually but not always associated with a depression of the heart's dynamic action and with electrocardiographic evidence of intraventricular block or damage. The slowing in these cases was a sinus bradycardia. In extreme form it preceded the death of the animal. These observations suggest that a slowing up of the heart rate following venesection should be considered a sign of danger. The applicability of this test should be tried clinically.

An asynchrony in the pressure rise of the curves obtained from the two ventricles was observed as well as in the onset and end of the ejection period. Some changes in the asynchrony were noted as the condition of the heart altered. The straddle of the left ventricular pressure curve was found to be consistently longer than the right although the difference in the straddle of the two curves varied.



On the other hand, the duration of ejection was longer as a rule, on the right side, indicating that the periods of isometric contraction and relaxation were shorter in the right ventricle. The duration of ejection of the two ventricles decreased after venesection and increased on distention of the heart. No consistent changes in the duration of ejection were found when the heart was overdistended. The greatest abbreviation of ejection occurred in the moribund heart.

Katz, L. N., and Brams, W. A.: Studies on the Overdistended Heart. II. The Rôle of Relaxation in Filling the Distended and Overdistended Heart. *Am. J. Physiol.* 98: 569, 1931.

In the course of these experiments a diastolic dip was seen resembling the one described in the isolated turtle heart by one of the authors when the heart was distended and overdistended. It was always observed in the right ventricular pressure curve and occasionally in the left. Its size in the right ventricular curve was a direct function of the diastolic size of the heart. The diastolic dip is not an instrumental artefact but expresses the pressure changes in the ventricle at this time. The dip is an exaggeration of the normal drop in the pressure present in the mammalian heart in the rapid filling phase and expresses an augmentation in the disparity between the rate of ventricular expansion and the rate of filling. An intraventricular pressure below atmospheric was never found in these experiments.

The diastolic dip indicates that ventricular relaxation plays a rôle in filling the mammalian heart by exerting an aspirating action during the rapid inflow phase.

Barrier, Charles W.: Tachycardia. *Ann. Int. Med.* 5: 829, 1932.

Important features in a series of 26 cases of supraventricular tachycardia are noted. Cases of unusual duration are reported, one having an attack lasting three years, another being in a permanent attack for nearly six years unless treated.

Quinidine in most cases of supraventricular tachycardia is the more desirable drug for arresting an attack; though in the presence of heart failure digitalis will act and may be the drug of choice. In two cases where quinidine was continued for a year, it had to be used in increasing doses. Continuous digitalization has been extended for a period as long as one and a half years. While the continuous use of digitalis is to be preferred over quinidine, the drug must be used in such large doses that toxic effects appear.

Both digitalis and quinidine will slow the rate and arrest the attacks in the same patient. Until the mechanism of these attacks is better known, the mode of action of drugs cannot be explained. Digitalis did not arrest an attack in a patient who had received 1/15 grain of atropine. Both digitalis and quinidine act well by mouth and few cases need the drugs by vein.

Blackford, L. Minor, and Booth, William Telford: Dextrocardia Secondary to Eventration of the Diaphragm. *J. A. M. A.* 98: 883, 1932.

A case of congenital dextroposition of the normal heart without evidence of transposition of other viscera secondary to eventration of the diaphragm in an athletic youth is reported.

The condition had been entirely asymptomatic up to the present, and it is believed that the position of the heart will never cause the patient any trouble. It is possible, however, that subphrenic symptoms may develop or that an extraordinary increase in intraabdominal pressure, brought on by trauma or tremendous exertion, may result in rupture of the weakened diaphragm.

Master, A. M., and Jaffe, Harry: Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever. The Differential Diagnosis. J. A. M. A. 98: 881, 1932.

In 17 patients with rheumatoid (infectious) arthritis, on whom electrocardiograms were taken daily for an average of fifty-three days, only the slightest evidence of myocardial involvement was recorded. In 63 cases of acute rheumatic fever, however, definite electrocardiographic evidence of myocardial involvement appeared in 100 per cent. These electrocardiographic evidences of myocardial involvement have been sino-auricular block, nodal rhythm, interference of the sinus and auriculoventricular nodes, auricular fibrillation, auricular flutter, auriculoventricular (P-R) intervals of 0.21 second or more, heart block with dropped beats, definite R-S-T abnormalities, T-wave inversions and transient widening, notching and slurring of the QRS group. It is concluded from these studies that rheumatoid arthritis, no matter what it may be, is not especially a disease of the heart; acute rheumatic fever is preeminently a carditis.

If there is no electrocardiographic evidence of myocardial involvement in a patient with joint symptoms, it would be best to suspect rheumatoid arthritis; whereas, when there are electrical tracings definitely indicative of myocardial involvement, it is probably due to an acute rheumatic fever.

Barnes, Arlie R., and Ball, Ralph G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations. Am. J. M. Sc. 183: 215, 1932.

In 1,000 unselected consecutive postmortem examinations more or less localized myocardial infarction was recognized grossly in 49 subjects. Of 685 of these subjects, forty years of age or more, myocardial infarction was observed in 47. The majority of the subjects who had sustained myocardial infarction had had associated hypertension as judged by the cardiac weights and the records of blood pressure.

Notable preponderance of arteriosclerosis in the left coronary artery over that found in the right was not observed in the hearts in which evidence of infarction was found. Gross myocardial infarction resulting from coronary occlusion was practically confined to the left ventricle. Myocardial infarction was observed in the posterior basal portion of the left ventricle in 24 instances as compared with 28 instances in which it involved the apex and anterior portion. More careful pathological study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region be not overlooked.

In 28 instances infarction occurred in the region supplied by the anterior descending branch of the left coronary artery, as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. The designation of the anterior descending branch of the left coronary as "the artery of coronary occlusion" is no longer justifiable.

Ellis, Laurence B.: Studies in Complete Heart-Block: II. A Clinical Analysis of 43 cases. Am. J. M. Sc. 183: 225, 1932.

An analysis is presented of 43 cases of complete auriculoventricular block in patients ranging in age from nine weeks to seventy-eight years. Seventy per cent of the patients were over forty years of age and the same percentage were males. In 29 cases the block was permanent, while in the remainder it was intermittent or temporary. Fifty-two per cent of the cases of permanent block were due to arteriosclerosis; 31 per cent were of undetermined origin but in most of these instances were probably either congenital or dependent upon an acute infection. Diphtheria, syphilis and rheumatic infection were responsible for a small number

of cases. Digitalis was the chief etiologic agent producing transitory block; although arteriosclerosis and infections caused a lesser proportion.

Complete heart-block per se may exist for very prolonged periods of time without damaging the health of the patient. Four cases are recorded in which the block is known to have existed for twenty-four, fifteen, fourteen and seven years respectively, and 2 more in which it has almost certainly lasted nine years. The chief factors governing the prognosis appear to be etiology, age, Adams-Stokes seizures, electrocardiographic abnormalities and cardiac size.

A discussion of the significance of arterial blood pressure findings is presented. Young persons with complete heart-block may have essentially normal blood pressures. A systolic arterial hypertension and wide pulse pressure usually occur in heart-block in persons giving evidence of peripheral arteriosclerosis.

**Gouley, Benjamin A., and Eiman, John: The Pathology of Rheumatic Pneumonia.**  
*Am. J. M. Sc.* 183: 359, 1932.

Nine cases of acute rheumatic fever are presented with reference to their pulmonary pathology. Eight of these showed an acute inflammation of lung tissue with consolidation; the ninth showed pleurisy with subacute lung involvement. All of them were associated with acute rheumatic heart disease. The inflammatory pulmonary reaction consists of an interstitial perivascular exudate of large endothelioid cells, identical in morphology with those found in rheumatic heart lesions and considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate are prominent features. Eight of these cases exhibited pericarditis.

**Wetherby, Macnider, and Clawson, B. J.: Chronic Arthritis With Special Reference to Intravenous Vaccine Therapy.** *Arch. Int. Med.* 49: 303, 1932.

Intravenous streptococcal vaccination brings about in patients two conditions (desensitization and a high agglutinating titer) that are regularly associated with the protection experimentally developed in animals against streptococci by intravenous vaccination. This analogous condition in vaccinated animals and patients affords a basis for intravenous vaccination in patients having chronic arthritis. Since subcutaneous injections of streptococci in animals tend to increase hypersensitiveness and only produce a low agglutinating titer in the serum, the subcutaneous method of vaccination in chronic arthritis would seem to be of less value than the intravenous method if not contraindicated. No ill effects have resulted from the intravenous vaccinations in the 100 cases studied. On the other hand, in 75 per cent of the cases the clinical improvement appears to be sufficient to justify the further use of this method of treatment for chronic arthritis.

**Goldring, William, and Chasis, Herbert: Thiocyanate Therapy in Hypertension. I. Observations on Its Toxic Effects.** *Arch. Int. Med.* 49: 321, 1932.

Of the 50 patients with hypertension in this series treated 74 different times with thiocyanate, 13 presented toxic manifestations. In 11 of these the toxic manifestations disappeared within a few hours to four days after discontinuance of the drug. Two of these patients died as the result of thiocyanate poisoning.

The frequency and order of appearance of the various toxic manifestations are noted. A fall in the blood pressure, the occurrence of toxic manifestations and death were found to be unrelated to the amount of thiocyanate administered or to the amount of residual drug in the body. Data are presented showing that in some patients there is little or no margin of safety between the toxic and thera-

apeutically effective dose of thiocyanate. Tissue analysis for thiocyanate and necropsy observations are presented in one of the fatal cases.

**Schwartz, Sidney P.: Transient Ventricular Fibrillation. A Study of the Electrocardiograms Obtained From a Patient With Auriculoventricular Dissociation and Recurrent Syncopal Attacks.** Arch. Int. Med. 49: 282, 1932.

A study was made of the electrocardiograms of a patient with auriculoventricular dissociation who suffered from sixty-seven seizures of unconsciousness during a period of seven months. Each seizure was associated with periods of ventricular fibrillation. The longest recorded attack with spontaneous recovery lasted six minutes and two seconds.

The alterations in the electrocardiograms preceding a syncopal seizure consisted of a gradual acceleration through steplike progressions of both the basic auricular and the ventricular rates, the highest regular ventricular rate recorded being 65.2 beats per minute before ventricular fibrillation set in. Periods of re-excitation of from 4 to 11 beats at a time were observed to appear during the premonitory period, heralding the approach of a seizure of unconsciousness. The onset of every recorded seizure of ventricular fibrillation in this patient was initiated by a ventricular extrasystole which was always of the same character and arose from the same focus in the ventricle.

The ventricular rates during the periods of ventricular fibrillation varied from a minimum of 250 to a maximum of 1,000 beats per minute. Spontaneous revival usually coincided with the cessation of ventricular fibrillation. The mode of recovery was variable, but the restoration of the basic rhythm was preceded by an idioventricular rhythm, with a slightly irregular ventricular rate following, as a rule, a postundulatory pause.

Periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto. A clinical diagnosis of transient ventricular fibrillation may be suspected in such patients if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate.

**Dawson, Martin H., Olmstead, Miriam, and Boots, Ralph H.: Bacteriologic Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid Arthritis.** Arch. Int. Med. 49: 173, 1932.

One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis according to the technic of Cecil, Nicholls and Stainsby. As control material, 31 samples of blood from normal persons and 16 samples of sterile autoclaved agar were subjected to similar manipulations. Blood cultures on patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance. No significant difference was observed in the bacteria encountered in the blood cultures of patients and those observed during the culture of the control material under similar conditions.

*Streptococcus viridans* was occasionally encountered during the culture of the control material as well as during the culture of specimens of the patients' blood.

Aerobic and anaerobic cultures of 23 specimens of synovial fluid obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance. Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

Criep, Leo H.: *The Effect of Bronchial Asthma on the Circulation.* Arch. Int. Med. 49: 241, 1932.

A complete cardiovascular survey of fifty patients suffering from bronchial asthma is presented. An electrocardiographic study of the acute asthmatic attack in eight patients is reported.

From these studies bronchial asthma apparently does not have a permanent damaging effect on the cardiovascular system. Acute attacks may as the result of the associated asphyxia produce minor transitory disturbances in cardiac conduction.

Schlesinger, Bernard: *A Study of the Sleeping Pulse Rate in Rheumatic Children.* Quart. J. Med. 1: 67, 1932.

A study of the alert pulse rate is not sufficient to establish the presence of active carditis in afebrile children with rheumatic heart disease. Normally, the sleeping rate is on an average of ten beats per minute slower than the alert pulse.

A rapid alert pulse rate unaccompanied by a similar increase in the rate during sleep, points to a nervous tachycardia. Active carditis can be presumed if in the absence of fever, the sleeping pulse rate approximates the alert rate so as to diminish or abolish the normal variation between the two. A sleeping pulse rate continuously and decisively above the normal is also strong evidence of active heart disease, even though the variation between the rates during sleep and wake persists.

Bradley, W. H. L.: *Epidemic Acute Rheumatism in a Public School.* Quart. J. Med. 1: 79, 1932.

Two epidemics of rheumatism are recorded, and their relation to parallel waves of hemolytic streptococcal sore throat is demonstrated, the causal streptococci being of two distinct strains.

Survey of the epidemiological factors concerned leads to the conclusion that droplet infection was responsible for the spread of sore throat and consequently of rheumatism. It is tentatively suggested that rheumatism occurred in those who, being incompletely immunized by a first contact with a rheumatism producing streptococcus, developed hypersensitiveness to that organism.

Campbell, Maurice, and Shackle, J. W.: *A Note on Aortic Valvular Disease.* Brit. M. J. 1: 328, 1932.

In a series of cases with disease of the aortic valves, the condition was due to rheumatism in 200, to syphilis in 55, to asthma in 20 and to all other causes in 21 cases. Out of every 6 rheumatic cases roughly, three had aortic incompetence and mitral stenosis, one had both with aortic stenosis as well, one had aortic stenosis and incompetence and one had aortic incompetence alone. Where there was no mitral disease, there were two men for each woman; where there was mitral disease, there were two men for every three women. They came under first observation at all ages, less commonly before ten or after fifty years. There was so little difference between the ages with and without aortic stenosis that its presence must depend on the severity and nature of the attack rather than on the length of time that had elapsed. Pure aortic stenosis was rarely found, and as far as could be judged from the pulse pressure, the stenosis was relatively unimportant compared with the regurgitation even where the signs were well marked.

Among the syphilitic cases, there were three men for each woman, nearly four-fifths being between forty and sixty years. Aortic stenosis was rarely ever

present, and the average pulse pressure was much greater than in the rheumatic cases.

Nearly all the atheromatous cases were men between fifty and eighty years. Aortic stenosis was more important and more frequently present, and signs of regurgitation were often absent.

Auricular fibrillation was present in 30 per cent of those who also had mitral stenosis, in 8 per cent of the rheumatic cases without mitral stenosis, and only rarely in the nonrheumatic group. Left ventricular preponderance was found in about half the electrocardiograms of those with pure aortic disease, normal limits being found in the remainder. The T-waves were inverted, most often in Lead I, in about one-quarter of the rheumatic cases and in about half the others.

The prognosis was enormously better in the rheumatic group. The average duration of life after the development of aortic incompetence was probably twenty years, excluding those who died quickly from active rheumatic carditis. In the syphilitic group, on the other hand, it was not much more than two years after the development of symptoms, few patients living for eight years.

Ellis, Laurence B., and Weiss, Soma: A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-Arterial Injection of Acetylcholine. *J. Pharmacol. and Exper. Therap.* 44: 235, 1932.

A study was made of the effect of the continuous intravenous injection of acetylcholine in 17 normal human subjects and of the intra-arterial injection in 4 normal subjects. During intravenous injection the following observations were made: The action of the drug was found to be transient, since a given rate of injection could be maintained for a prolonged period of time with no evidence of cumulative action, and since the effects disappeared very rapidly following cessation of the injection. The rate of injection necessary to produce minimal effects was between 0.02 and 0.06 gram per minute, and the maximum tolerated dose was an amount given at a rate of between 0.09 and 0.14 gram per minute. The largest total amount injected was 1.0 gram in ten minutes.

The symptoms produced were flushing of the head and upper part of the body, throbbing in the head, palpitation, sweating, salivation, lachrymation, substernal constriction, nausea and vomiting.

Either no effect or a slight rise in the cardiac rate occurred. In only 3 of 13 cases was there any appreciable lowering of systolic or diastolic arterial blood pressure. In 5 cases in which cardiac minute volume outputs were estimated, no significant change was observed. In each of 5 instances there was a slight increase in the basal metabolic rate.

During the intra-arterial injection of acetylcholine there was marked regional dilatation of the arteries and arterioles, as evidenced by flushing, increase in skin temperature, increased arterial pulsation and increased blood flow. Evidence was found that this increase in blood flow continued for nearly thirty minutes following the cessation of the injection, although the symptoms and flush disappeared much more quickly. That is, although the destruction of the drug in the body was almost instantaneous, the effects of its action persisted for some time. No general systemic effect was noted following the intra-arterial injection of the drug.

It is suggested that the inactivation of acetylcholine probably occurs during its passage through the capillaries. The effects of acetylcholine administered intravenously to man and anesthetized animals are qualitatively similar, but man is very much more tolerant to the drug than are animals.

The theory that acetylcholine acts as a general hormone in the human body and normally circulates in the blood stream is unlikely. Unless acetylcholine acts in

disorders of the arteriolar system differently than in normal subjects, it cannot be considered a useful therapeutic agent in such conditions.

Krogh, A., Turner, A. H., and Landis, E. M.: *A Celluloid Capsule for Measuring Venous Pressures*. J. Clin. Investigation 11: 357, 1932.

A celluloid capsule for the determination of venous pressures is described. This capsule is very easily made, and notches can be cut so that it will fit any arrangement of veins. It is cemented to the skin with collodion. When with high venous pressures the necessarily high intracapsular pressure would cause distortion of the skin and erroneous readings, the error can be avoided by the use of a counterweighting clamp also described. Such a counterweight is usually needed for the measurement of venous pressures above 30 cm. water pressure.

Harrison, T. R., Calhoun, J. A., Cullen, G. E., Wilkins, W. E., and Pilcher, C.: *Studies in Congestive Heart Failure. XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing*. J. Clin. Investigation 11: 133, 1932.

Studies have been made of the respiratory rate and depth, the minute ventilation, and of the oxygen, carbon dioxide and  $P_H$  of the arterial blood and of the venous blood from the brain of dogs anesthetized with barbital. In some experiments artificial reduction of vital capacity was produced either by pneumothorax, by introducing fluid into the lungs through the trachea, or by distending the capillaries of one lung with blood, according to a technic which has been described. In other experiments observations were made concerning the sensitivity of the respiration to oxygen lack, carbon dioxide excess and to acidosis produced by the intravenous injection of ammonium chloride. The following results were obtained.

Reduction of vital capacity by any of the methods used resulted in rapid breathing, provided the vagus nerves were intact. In such experiments chemical changes of the blood were usually either absent or in the direction of increased alkalinity.

In some vagotomized dogs diminution in vital capacity was usually not followed by rapid breathing, unless the diminution was of sufficient degree to produce either marked oxygen lack or increased acidity of the blood.

Oxygen lack produced by rebreathing caused increased ventilation by increase in either depth or rate, or both. In order to double the ventilation it was usually necessary that the arterial blood be less than 60 per cent saturated.

Carbon dioxide excess caused marked increase in depth and relatively slight increase in rate of breathing. The response of the animals to carbon dioxide excess was quantitatively greater and qualitatively different from that of oxygen lack. In order to double the ventilation it was usually necessary to produce a fall of approximately 0.10 in  $P_H$  and a rise of 10 mm. Hg in carbon dioxide tension of the arterial blood.

The effect of the acidosis produced by ammonium chloride on the breathing was unlike that of carbon dioxide excess and rather similar to that of oxygen lack, being characterized by a relatively great increase in rate and only slight increase in depth. Following the injection of ammonium chloride apnea sometimes occurred.

Chemical changes in the blood never produced the extreme degree of tachypnea which resulted from diminished vital capacity.

Vagotomized dogs, although insensitive to diminution in vital capacity, reacted with increase in ventilation to chemical changes in the blood.

From these observations the following conclusions have been drawn.

Orthopnea and the continuous dyspnea at rest which occurs in the terminal stages of cardiac disease are of reflex origin and dependent on diminished vital capacity.

It is probable that the rapid breathing found in various diseases of the thoracic organs accompanied by decrease in vital capacity is essentially of reflex origin.

The reflex mechanism of respiratory control is more sensitive than the chemical mechanism. The respiratory center seems to be much less sensitive to alteration in the composition of the blood than has been generally believed.

Krogh, A., Landis, E. M., and Turner, A. H.: The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood. *J. Clin. Investigation* 11: 63, 1932.

The movement of fluid through the human capillary wall was studied by means of a pressure plethysmograph, which collapsed the blood vessels and thus permitted the accurate determination of small changes in tissue volume. It was shown that within certain limits the determination of volume change was not significantly influenced by hyperemia or by previous engorgement of the veins. Fluid accumulated in the tissue spaces when venous pressure was greater than 15 or 20 cm. water. Above an average venous pressure of 17 cm. water, the rate of filtration was directly proportional to the increase in venous pressure. A unit rise in venous pressure (1 cm. water) increased the filtration rate by 0.0023 c.c. per minute per 100 c.c. of arm.

The rate at which fluid was removed from the tissue spaces depended on the size of the accumulation of fluid, being distinctly more rapid with large amounts. When less than 0.6 c.c. of fluid per 100 c.c. of arm was present, the removal of fluid was retarded by elevating venous pressure to 15 or 20 cm. water, which was taken to indicate that small amounts of fluid were removed chiefly by true absorption. When more than 0.6 c.c. of fluid per 100 c.c. of arm was present, the fluid was removed in spite of slight grades of venous congestion. In this connection the relative importance of tissue turgor and lymphatic drainage is briefly considered.

When the colloid osmotic pressure of the blood was elevated by standing, the rate of filtration produced by a given venous pressure was uniformly lower. A unit rise of colloid osmotic pressure (1 cm. water) was accompanied by a fall in filtration rate varying between 0.0027 and 0.0045 c.c. per minute per 100 c.c. of arm.

The observations are discussed with reference to capillary pressure and fluid balance in man.

Payne, Sheldon A., and Peters, John P.: The Plasma Proteins in Relation to Blood Hydration. VIII. Serum Proteins in Heart Disease. *J. Clin. Investigation* 11: 103, 1932.

In patients with heart failure serum albumin is frequently reduced. Although edema of heart failure may occur even when serum protein and serum albumin are at or above the normal level, it is more commonly associated with some degree of albumin deficiency. The albumin deficits appear to be directly referable to malnutrition.

Gallavardin, L., and Veil, P.: A Case of Permanent Bradycardia with a Rate of Forty. *Arch. des Maladies du Cœur*, 1928, iv, 210.

The author reports the case of a man of sixty-one years with hypertension following two attacks of hemiplegia and pseudo bulbar signs. The pulse rate at this time was 40 per minute, sometimes lower; except for a rare irregularity, the rate was regular. Amyl nitrate and effort made no difference in the bradycardia.



Auscultation revealed a periodic increase in the vibratory and booming qualities of the heart signs due to the superposition of auricular and ventricular contractions.

The electrocardiogram showed an auricular ventricular sequence but the relation between auricular and ventricular complexes varies constantly. Sometimes before, sometimes superposed and sometimes following the ventricular complex. When the distance between the ventricular and auricular complex was great, the ventricle regained its irritability and a contraction occurred with the appearance of bigeminy. Normal rhythm was restored with subcutaneous injection of .01 gm. of pilocarpine nitrate.

In this case, one could eliminate such diagnosis as partial or total block and sinus bradycardia with ventricular escape.

Two interpretations were considered: first, nodal rhythm with an upright P-wave. The slow rate, the constancy of the association between auricular and ventricular make it resemble permanent nodal rhythm. In the tracing, P-wave first preceded QRS, then was superposed, then followed it, and the only difference between this and nodal rhythm was that the P-waves were uniformly upright. Because of this factor the authors do not think it is a case of nodal rhythm. Second, a possible interpretation is an arrhythmia of the entire A-V cycle. Admitting it only as a hypothesis, the authors based their belief on the constancy of this association of the auricles and the ventricles.

They consider whether some higher center might be responsible for this altered rhythm and attempt to correlate it with the pseudobulbar palsy of the subject.

**Geraudel, E.: Paroxysmal Tachycardia.** Arch. de Malad. du Coeur, 1928, v, 273.

The author cites two cases of paroxysmal tachycardia of long duration. Both cases could have been mistaken for the auricular ventricular form of the condition were it not for the electrocardiograms taken during freedom or comparative freedom from attacks. In both instances, the tracings made during the crises showed a position of the P-wave closer to the preceding R-wave than to that following. This gives the impression of nodal rhythm.

During the intervals between attacks, flutter with a varying auricular to ventricular ratio was present. 2:1 in the case of 1 subject and 2:1 to 3:1 in the case of the other. During a period where attacks were followed by periods of freedom, the auricular rhythm was constant while that of the ventricle became grouped in series of 2 and 3 and 4 ventricular beats. This quadrageminy was shown to merge easily into that of paroxysmal tachycardia; as it did so the P took a position closer to the preceding R than to the one following.

The author concludes that paroxysmal tachycardia of auricular ventricular or sinus origin does not occur, both being phases of auricular tachycardia or flutter where there is an iso-arrhythmia of auricle and ventricle. No new centers dominate the rhythm, but rather a variation was present in the harmony of the response of the auricles and ventricles.

**Geraudel, E.: Auricular Tachysystole and Auricular Fibrillation,** 1928, v, 289.

In a second paper, the author attempts to show that the difference between auricular flutter and fibrillation is only one of degree. The definition of flutter as a condition with a rapid rate and a definite ratio between the auricular ventricular rate is not sufficiently exact. The author's definition is that of a rate more or less rapid and showing under prolonged observation a lack of co-ordination between the auricular and the lowered ventricular rates.

The term total arrhythmia for fibrillation is to be discouraged as it differs in the pulse and such an arrhythmia of the pulse may be produced by other conditions than fibrillation. The complexes resemble those of flutter and for these the term flutter fibrillation was used. This has been supposed to be a combination of the two arrhythmias, the periods of fibrillation depending on the change in the refract period of the muscle.

The author considers this to be wrong and based on the wrong assumption that changes in the form of the P-wave are due to changes in the excitation wave in the auricle. The P-waves of flutter may resemble those of fibrillation by other influences and so be recorded by the string. The abnormal shape of the P-wave in the fibrillation periods may be due to a rapid rate, for although fibrillation waves may be present with an apparent rate of 75, they are commoner with the auricle beating between 400 and 600 per minute. Two facts are evident in the study of fibrillation—the rapid rate and the inconstancy of the rhythm.

The author therefore considers the difference between auricular flutter and fibrillation is that in the former the rate is 130 to 400 and constant, while in the latter it is 475-600 and variable. He suggests that the term tachyatrie monorhythmique for flutter and for fibrillation the term hypertachyatrie poikilorhythmique.

## Book Reviews

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DER HERZALTERNANS. By Bruno Kisch. Dresden and Leipzig, 1932, 214 pp., Theodor Steinkopff.

Dr. Kisch, Professor of Physiology at the University of Cologne, presents a most comprehensive study of the difficult and complicated subject of alternation of the heart. He not only has studied the literature thoroughly, but has carried on experimental work for twelve years.

The author devotes the first third of the volume to a brief discussion of what the term means and to a detailed consideration of the various methods—physical, graphic and electric—by which alternation has been studied. He then describes and illustrates seven different disturbances which may produce alternation, namely, alternating partial asystole or hyposystole, alternating partial hypodiastole or adiaastole, alternating asystole and adiaastole of different parts of the heart muscle, alternation of total systole, alternation of impulse formation or conduction, and alternation of the filling and emptying of the heart produced by hemodynamic factors. He believes that in the last analysis an understanding of this complex subject will depend upon an understanding of chemical and physicochemical changes in the heart muscle. In the section devoted to factors which affect alternation the author discusses inherent properties of heart muscle, the influence of various salts and poisons, rate, extrasystoles, conduction, the coronary circulation, temperature, and the cardiac nerves. Finally he discusses, relatively briefly, the relationship between alternation and other disturbances of the circulation and the clinical features. He provides twelve pages of references and a carefully prepared index.

This study, which must represent a tremendous amount of work, is of scientific rather than clinical interest. The bibliography alone would be valuable to anyone interested in the subject, and the subject will remain open until the chemical and physicochemical properties of heart muscle which Dr. Kisch stresses are much more fully understood.

E. H.

DER WASSERVERSUCH ALS NIERENFUNKTIONSPRÜFUNG. Von Dr. Med. Ferdinand Lebermann, Fachartz für Innere Krankheiten in Würzburg. Dresden und Leipzig, 1932, pp. 145, Theodor Steinkopff.

In this study not only is the attempt made to determine the advantages and limitations of the dilution and concentration tests (as they are generally called in this country), but also these tests are used as a means of approaching the intricate problem of water balance and metabolism in the body. The questions at issue touch various phases of Bright's disease especially, but are not restricted to this disease; the discussion extends to diabetes insipidus.

In considering the various theories of water excretion through the kidney the author seems to find himself cramped, since it is not always easy to harmonize experience in the clinic with any theory so far propounded. There is throughout the essay a constant reference to extrarenal factors which in some relations only are known at present. Specifically is cited the observation of Marx, that the ingestion of relatively small amounts of water induces as much "dilution" of the blood when measured by hemoglobin changes as does the ingestion of large amounts, and further, that there seemed only a remote relation between degrees of blood dilu-

tion and maximal urine excretion. Lebermann studies this question of water content of the blood along with the volume of urine excreted hour by hour during the dilution and concentration tests.

In American clinics the selection of even quite accurate hemoglobin estimations as a means of determining the water content of blood (or more probably blood volume), would be regarded as unfortunate.

Lebermann uses the dilution test in the conventional manner of Volhard and Strauss, except that one liter, rather than a liter and a half, of water (or tea) is given to the fasting patient, and the urine is collected hourly for four hours. The concentration test is carried out during the afternoon of the same day; a sequence which has been much criticized and largely abandoned in this country. From these two tests information may be gained bearing on the functions of excretion, dilution and concentration. In Lebermann's opinion impairment of concentration is the chief diagnostic point.

About one-half the monograph is devoted to the study of various types of Bright's disease by means of these tests. The theoretical assumption that according to the location of the lesion in the kidney the water test should demonstrate typical disturbances in the renal capacity for excretion, dilution or concentration does not work out perfectly; differential diagnosis is accurate only within certain limits. For example, a case of nephrosis with variable edema gave responses resembling acute glomerulonephritis with dropsy. In acute glomerulonephritis of the post-anginal type the dilution and concentration tests were practically normal, indicating, it was assumed, extrarenal factors. Likewise, with cases of early chronic glomerulonephritis and also with nephrosclerosis, the tests may fail to give results which are essentially informing.

The attempt to use these tests as a means of recognizing various types of Bright's disease is based on dubious reasoning. In so far as they are of value, they measure the degrees of defect, and to assume that a degree of defect is peculiar to a type of renal disease, and is specific, is not in harmony with what is known today. Moreover, the tendency of recent years is to regard nephritis less and less as a disease of the kidneys, but rather as a constitutional disorder in which the kidneys are implicated; hence the return of recent writers to the term Bright's disease.

In order to estimate extrarenal factors, particularly cardiac, and also to find a method of using the dilution and concentration tests in prognosis, Lebermann had recourse to the use of diuretic drugs along with the Volhard test. The drugs used range from digitalis through diuretin and urea to salyrgan. The author derived an encouragement from his experience which the reviewer cannot share.

There is an extensive bibliography which omits several relevant English and American names.

N. B. F.

LE NEUROSI DEL CUORE E DEI VASI SANGUIGNI E LORO CURA. By Professor Giovanni Galli (University of Pavia) Milan, Societa Editrice Libreria, 1930, pp. 361.

(*The Neuroses of the Heart and Blood Vessels and Their Treatment*) In this lucidly written book Professor Galli presents his ideas and observations concerning the functional disturbances of the circulatory system. He speaks of their increase in modern times with the comment that a true civilization is one which should prevent illnesses rather than cause them.

He gives an historical account of various treatments of the neuroses throughout the ages, beginning with those employed in the temples of Aesculapius, continuing on through mesmerism, osteopathy, Christian Science, Couéism, and finally psychoanalysis.

He considers the influences of diets, poisons, drugs and hormones on the heart and blood vessels. He classifies and describes the various tachycardias, and considers in turn extrasystoles, palpitations, mitral neurosis, respiratory arrhythmias, hypotension and hypertension on a neurotic basis, and then discusses visceral, skin and arterial vasomotor disturbances, and finally the circulatory neuroses on a sexual basis.

He treats occurrences, causes and medications in a well-ordered, interesting manner, guided by a sound insight and well-balanced evaluations.

While considering psychoanalysis of the greatest value in treating the neuroses, he pays due regard to the use of medical and surgical therapies.

The author's definition of a neurosis is of special interest. He says: "A neurosis is a disease of the small blood vessels accompanied by both physical and chemical lesions which are, as a rule, completely curable. The signs and symptoms, diverse in character, vary according to the organ or part in which the attendant circulatory disturbance occurs: Psychic influences play an important rôle." He considers such an interpretation a working point for research, and one which further investigations will substantiate, rather than one already proved. He admits the lack of instruments and objective proofs to support this viewpoint in most cases, but calls attention to the fact that in accessible organs these proofs are not wanting, as may be seen in the vessels of the eye, larynx and extremities.

He quotes Sawitzky, (*Ztschr. f. Kreislaufforsch.* 1929, 1) who in his experiments in cases of mitral neurosis has shown evidences of spasm in the papillary muscles of the heart as the cause of incomplete occlusion of the mitral valves.

In addition the book contains excellent anatomical and physiological considerations, interesting case reports, and a description of the technic of psychoanalysis.

A. R. B.

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## Original Communications

### APICAL SYSTOLIC MURMURS IN CHILDREN

#### FOLLOW-UP OBSERVATIONS IN 100 CASES\*

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THE question of the importance of apical systolic murmurs is one of the difficult problems confronting the physician. Such murmurs are discovered in most cases first by the school physician who sends the child home with a statement that heart disease is present. The parents, greatly perturbed, consult the pediatrician or the family physician. He examines the child, finds the systolic murmur at the apex with little or no evidence of other cardiac changes, tells the parents the child will outgrow the murmur and thus allays their fears to some extent. If a cardiologist is consulted he has little more to offer, although in his own mind he may be somewhat uncertain of the final outcome. Such uncertainty arises because there has been no accurate study made of the progress of such murmurs over a period of years.

There are certain orthodox rules to which the cardiologist may adhere when determining whether the apical systolic murmurs are of organic nature. If the murmur is well transmitted and associated with hypertrophy and fluoroscopic evidence of mitral disease, it is usually considered organic. Or he may follow the criteria of Mackenzie<sup>1</sup> who states that if we find a systolic murmur in a good functioning heart of normal size and rhythm with the absence of anything that would indicate that the murmur is definitely organic in nature, then we may conclude that the heart is perfectly normal. Granted that we could decide absolutely which murmurs are organic and which are not, we should still be unable to give any definite prognosis because it is known that organic mitral insufficiency per se rarely if ever causes cardiac embarrassment. The patient and the doctor are most interested in knowing what the future will bring; will the murmur disappear; will there be complications in the form of mitral stenosis; how long will the patient be able to continue with activity unrestricted?

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A search of the literature reveals innumerable opinions as to the subsequent course of apical systolic murmurs, but these opinions have not been based on followed cases. Most men are in accord with the statement that systolic murmurs at the apex are not reliable evidence of heart disease. Cabot,<sup>2</sup> in fact, does not believe that pure mitral insufficiency can be recognized during life as a clinical entity. Reid<sup>3</sup> finds systolic murmurs in 20 per cent of the university students classified as normal. Fahr<sup>4</sup> finds that 40 to 70 per cent of all children between the ages of six and fourteen years and 35 per cent of otherwise normal individuals in the second decade have systolic murmurs. He states further that if no diastolic murmur appears during one or two years following the last attack of rheumatic fever, and if the size and shape of the heart have not changed significantly, the murmur is probably of no significance. Many of these murmurs are admittedly of no significance, but a certain number do progress to advanced cardiac conditions. In an effort to solve the problem as to how many will ultimately become significant, and if possible to establish criteria whereby we may be able to judge which murmurs will be of significance, we have undertaken this study of 100 cases followed over a period of years.

For the purposes of this survey the patients studied were limited to young persons with uncomplicated systolic murmurs at the apex, either accompanying the first sound or replacing it. Patients showing any other pathological processes, such as acute febrile diseases, nephritis or congenital heart disease, were excluded.

Examinations of the patients reported were made in the cardiac clinic of Mt. Sinai Hospital by the same group of men. Most frequently the patients studied were sent to the Cardiac Clinic by the pediatric department because of the discovery of a systolic murmur.

In this series a complete history of the preceding infections was obtained in all cases studied. After a complete physical examination in which the condition of the cardiovascular system was stressed, an orthodiagram and an electrocardiogram were made. These were repeated at the time of the last examination wherever possible. There were 49 females and 51 males in the survey. The youngest was 2 years of age and the oldest 21 years of age. Seven of the patients were 5 years of age or under, 85 were between 6 and 15 years of age, and 8 were between 16 and 21 years of age. The average age was 10.15 years. The average number of years the patients were followed was 6, while the greatest number of years followed was 15. The cases chosen for the study all had fairly loud apical systolic murmurs, without other complicating murmurs.

There were 2 deaths (2 per cent) during the observation period, one occurring after 8 years of observation, and another after 7 years. The first of these died of subacute bacterial endocarditis, and the second of

pneumococcus meningitis. Neither of these showed signs of cardiac failure.

Seventeen (17 per cent) of the patients developed distinct clinical evidence of mitral stenosis. The earliest case of mitral stenosis was discovered one year after the finding of the systolic murmur. The average development of mitral stenosis occurred 4.7 years after the discovery of the systolic murmur. The criterion for the diagnosis of mitral stenosis in all instances was a distinct presystolic or diastolic murmur at the apex with or without other accompaniments of the condition. In other words, the diagnosis of mitral stenosis was not made unless we were certain of its presence.

Nine patients (9 per cent) developed aortic insufficiency during the follow-up period. The earliest of these occurred two months after the apical systolic murmur was noted. The average development of aortic insufficiency occurred 3 years after discovery of the systolic murmur at the apex. The diagnosis of aortic insufficiency was made on the finding of a distinct diastolic murmur audible at the aortic area or along the left sternal margin.

Four patients (4 per cent) developed combined lesions of mitral stenosis and aortic insufficiency. The earliest of these appeared 3 years after the systolic murmur was discovered while the average appeared 5.2 years after the systolic murmur was noticed.

In all, 30 patients (30 per cent) developed serious valvular complications in the form of mitral stenosis, aortic insufficiency or both. Of the remainder, 60 patients (60 per cent) showed uncomplicated apical systolic murmurs, and 8 patients (8 per cent) showed complete disappearance of all murmurs at the time of the last examination. The small number of patients (8) showing disappearance of the murmur is contrary to the popular conception that the majority of apical systolic murmurs seen in ambulatory children disappear as they grow older. This may be due in part to the care taken in looking for these murmurs. (This information is summarized in Table I.)

TABLE I  
FOLLOW-UP FINDINGS IN 100 CASES OF APICAL SYSTOLIC MURMURS

|                               |             |
|-------------------------------|-------------|
| No murmurs                    | 8 per cent  |
| Uncomplicated systolic murmur | 60          |
| Advanced cardiac disease      | 30          |
| Mitral stenosis               | 17 per cent |
| Aortic insufficiency          | 9           |
| Combined                      | 4           |
| Deaths                        | 2           |

The relationship of the history of rheumatic fever, chorea and tonsillitis to the progress of the cases was studied. Twenty-six patients (26 per cent) gave a history of rheumatic fever. Of these, 5 developed mitral stenosis, 6 aortic insufficiency, 2 combined aortic insufficiency and



mitral stenosis, 10 continued with the apical systolic murmur, and 3 were found to be normal.

Of the 12 patients who gave a history of chorea, 6 developed mitral stenosis; one was found normal, and the remaining 5 continued with the systolic murmur.

In totaling the patients with a history of rheumatic fever or chorea we have 38 patients, 19 of whom developed serious cardiac complications. Therefore, given a history of chorea or rheumatism plus a systolic murmur at the apex we may anticipate a 50 per cent chance of serious cardiac disease.

Of the 17 patients giving a history of serious attacks of tonsillitis, without other rheumatic manifestations, 2 developed mitral stenosis, 2 developed aortic insufficiency, 12 remained with systolic murmurs, and one was entirely normal. Thus of 17 patients giving a history of serious attacks of tonsillitis, four (or 23.5 per cent) developed serious cardiac complications.

Of the remaining 45 patients (that is, those without history of rheumatic fever, chorea or definite attacks of tonsillitis) 4 developed mitral stenosis, one developed aortic insufficiency, one developed both mitral stenosis and insufficiency, 35 continued with systolic murmurs, and 4 became normal. Thus we have six patients (13.3 per cent) without any history of rheumatic fever, chorea, or tonsillitis who developed serious cardiac complications. (See Table II.)

TABLE II  
RELATIONSHIP OF HISTORY TO DEVELOPMENT OF SERIOUS CARDIAC  
COMPLICATIONS

|                            | PERCENTAGE DEVELOPING<br>SERIOUS CARDIAC<br>COMPLICATIONS |
|----------------------------|---|
| History of rheumatic fever | 50  |
| History of chorea          | 50  |
| History of tonsillitis     | 23  |
| No history of infection    | 13  |

These conclusions are in accordance with the findings of Morse<sup>5</sup> who states that in the cases in which rheumatism seemed to be the cause of the cardiac involvement the results were not so good as in the cases in which there was not a definite rheumatic history.

We have also attempted to ascertain whether the presence of fever during the course of observation could be used as a prognostic guide. Seventy patients were found to have had some elevation of temperature (usually between 99° and 100° F.) on at least 2 successive visits. Of these, twenty-five (36 per cent) developed mitral stenosis or aortic insufficiency or both, forty (57 per cent) remained with apical systolic murmurs (one of these, however, died of subacute bacterial endocar-

ditis), and five (7 per cent) showed complete disappearance of the murmur. Of the 30 patients who did not show any elevation of temperature, 6 patients (20 per cent) developed cardiac complication, 21 patients (70 per cent) remained with apical systolic murmurs, and 3 patients (10 per cent) showed complete disappearance of the murmur. We thus have not found the presence of slight elevation of temperature to be of much assistance to us in determining which of the cases would progress to serious cardiac complications.

Of interest is the fact that of the 7 patients 5 years of age or under only 1 developed mitral stenosis or aortic insufficiency, and this was a girl first seen by us at the age of 3 with an apical systolic murmur. This patient's course was uneventful until she had her first attack of chorea 5 years later at the age of eight, and then about 18 months after this she began to show signs of mitral stenosis. Also, 3 of these patients (45 per cent) showed complete disappearance of the murmurs later on. These findings tend to confirm the experience of many observers that systolic apical murmurs in very young children are of no serious significance.

We have also classified the patients according to whether their condition at the last examination was improved, unchanged, or worse, as compared with the first examination. This classification showed that 16 patients (16 per cent) were improved, 44 patients (44 per cent) were unchanged and 40 patients (40 per cent) were worse as far as their cardiac condition was concerned.

Of the 49 females, four have married and have had from one to four children each. One of these patients showed mitral stenosis at the last examination, two showed only a systolic apical murmur, while the third has no murmurs whatsoever.

Forty-three of the patients showed clinical enlargement of the heart at the time of their first visit. Of these, one died and 15 developed mitral stenosis or aortic insufficiency, while 2 patients showed no murmurs at all at the last examination. In other words 37 per cent of those patients showing clinical evidence of cardiac enlargement developed serious cardiac complications.

We next considered the value of the x-ray picture in the prognosis. In thirty patients the orthodiagram at the first examination showed the transverse diameter of the heart to be greater than half the diameter of the chest, that is, showed definite cardiac enlargement. Of these thirty cases, twelve (40 per cent) developed mitral stenosis or aortic insufficiency, two (6.7 per cent) died, while one (3.3 per cent) showed no murmur at the last examination. This checks closely with the clinical finding of enlargement, 37 per cent of those showing clinical enlargement and 40 per cent of those showing orthodiagraphic enlargement developing further cardiac complications.

At the first examination twenty-three of the patients were reported as having negative orthodiagrams, that is, no enlargement and no change in contour. Of these, only two (9 per cent) developed mitral stenosis. Of the remainder, four (18 per cent) showed no murmurs whatsoever, at the last examination, and three (13 per cent) were classified as unchanged at the final examination. From this we may conclude that a systolic murmur in the presence of a normal fluoroscopic examination has small chance (9 per cent in our series) of developing into a serious cardiac complication. This is in line with Berger's<sup>6</sup> findings of the importance of the orthodiagram in distinguishing functional from non-functional murmurs.

Electrocardiograms were taken in 76 patients (76 per cent). The P-R interval was found to be prolonged in only one case. There were eighteen instances of right axis deviation and four instances of left axis deviation, while the remainder of the records were essentially negative. The electrocardiogram was found to be of no value in estimating the prognosis.

By way of illustration we shall briefly outline a few of our cases.

CASE 1.—S. P., female, first seen May 20, 1924, at the age of eighteen years. No history of rheumatic fever, chorea, or tonsillitis. At this time the heart showed moderate enlargement to the left. There was an accentuated first sound at the apex, followed by a blowing, musical murmur. The orthodiagram at this time showed mitral configuration with slight enlargement of the left ventricle. The electrocardiogram showed right axis deviation. In October, 1929, a faint presystolic murmur was first heard, and in January, 1930, a faint diastolic murmur was also audible in the third interspace just to the left of the sternum. At the last examination, September 24, 1931, there were moderate cardiac enlargement to the left, a presystolic rumble at the apex, a tympanitic first sound, and a systolic murmur, also a to-and-fro murmur at the aortic area. The blood pressure was 136/60 mm. The patient was working full time as a teacher. During the entire period there were no rheumatic episodes.

CASE 2.—A. S., female, aged nineteen years, admitted October 7, 1922. She had had chorea four years previously. At the first examination there was a systolic murmur at the apex but no enlargement. There was no x-ray picture taken at this time, but in 1926 the x-ray examination showed mitral configuration with additional slight enlargement to left and right (diameter of chest 24 cm., transverse diameter of heart 13.5 cm.). The electrocardiogram was negative. In 1928 a diastolic rumble first appeared at the apex. The last examination, October 6, 1931, showed typical systolic and presystolic murmurs at the apex. She has had four pregnancies during this period.

CASE 3.—S. B., male, aged nine years, admitted April 13, 1926. At this time he was having choreic manifestations. At the first examination there was a systolic murmur at the apex, but no cardiac enlargement. The orthodiagram showed straightening of the middle left cardiac margin but no bulging of the left auricle in the retrocardiac space. (Diameter of chest 19 cm., transverse diameter of heart 9.5 cm.) The electrocardiogram was normal, except for an inverted P-wave in the third lead. In March, 1930, a presystolic murmur appeared at the apex. At the last examination, October 24, 1931, there were a presystolic thrill at the apex, presystolic and systolic murmurs at the apex, and moderate cardiac enlargement to the left. The orthodiagram at this time showed mitral configuration, with slight encroachment of the

left auricle on the retrocardiac space. Incidentally, this boy feels well and engages in school athletics.

CASE 4.—R. G., female, aged three and one-half years, admitted July 3, 1923. There was no history of rheumatic fever, chorea, or tonsillitis. Examination showed a blowing systolic murmur at the apex, transmitted out to the left axilla, but no cardiac enlargement. The orthodiagram at this time showed a transverse heart with no enlargement. (Diameter of chest 14 cm., and transverse diameter of heart 7 cm.) The course was uneventful and the last examination, November 14, 1931, showed no murmurs and very slight enlargement of the heart to the left. The orthodiagram at this time was essentially normal. (Diameter of chest 19 cm., and transverse diameter of heart 8.5 cm.)

#### SUMMARY

A follow-up study, covering an average period of six years, was made of 100 children with uncomplicated apical systolic murmurs, with the following results:

1. Of all the patients 30 per cent developed serious complications (mitral stenosis, aortic insufficiency or both).
2. Of those giving a history of rheumatic fever or chorea 50 per cent developed serious cardiac complications.
3. Among those showing clinical enlargement at the first examination 37 per cent developed serious cardiac manifestations.
4. Of those showing enlargement by orthodiagram 40 per cent developed serious cardiac manifestations.
5. Only 9 per cent of those with entirely normal fluoroscopic findings developed further evidences of cardiac disease.
6. Only 8 per cent of the patients showed complete disappearance of the murmur.
7. Only one of the seven patients 5 years of age or under developed serious cardiac complications and this patient had an attack of chorea at 8 years of age, following which she developed mitral stenosis.
8. The electrocardiogram seemed to be of no value in estimating the prognosis.

We wish to thank Drs. H. S. Feil and M. L. Siegel for their assistance in the examination of the patients and preparation of the paper.

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# ROENTGENOGRAPHIC STUDIES OF THE RIGHT VENTRICLE\*

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THE right ventricle is a chamber which is particularly difficult to examine by the usual clinical methods. There are many instances where definite information as to enlargement of this chamber is valuable, if not indispensable. Roentgenography of the right ventricle offers methods of study by which this information can be obtained in a sufficiently large proportion of cases to warrant its use as a routine clinical procedure.

Kirch,<sup>1</sup> in recent anatomical and physiological studies, has shown that each ventricle, the right as well as the left, consists of two physiological units, designated as inflow and outflow portions or tracts. That part of each chamber receiving blood from the auricles, formed by the area between the atrioventricular ostium and the apex, is called its inflow tract. The part of the ventricle concerned in expulsion of blood, lying between the apex and the arterial ostium, is called its outflow tract. Below, we shall attempt to show that parts of the inflow and outflow tracts of the right ventricle can be demonstrated radiographically.

It is to be understood that radiography of these tracts must be limited to those portions of the right ventricle which by proper rotation of the patient can be brought into position, so as to outline the contours of this chamber.

In a normal heart, in the usual postero-anterior position, the only part of the right ventricle visible in the cardiac contour is the pulmonic artery and a small part of the pulmonic conus. These are represented by the so-called second curve in the upper part of the left border. Below lies the curve of the left ventricle, and the junction is especially clear in fluoroscopy, where the outward thrust of the conus in systole is in contrast to the inward contraction of the left ventricle. This second curve, then, represents one part of the outflow tract of the right ventricle. It can be further emphasized by rotating the patient into the right anterior oblique position. This rotation brings out the conus and ventral portions of the right ventricle.

The inflow tract, that portion of the right ventricle lying between the atrioventricular ostium and the apex, is best seen in the left anterior oblique position. In this view the subject should be rotated sufficiently (at least 50°) so that the heart is clear of the spine. The lower part of the right cardiac silhouette and the major portion of the diaphragmatic outline will make up the inflow tract of the right ventricle (Fig. 1).

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In this position the body of the right auricle is rotated posteriorly, and the upper part of the right cardiac silhouette is formed by the right auricular appendix (Koch and Wieck<sup>2</sup>) (Fig. 2).

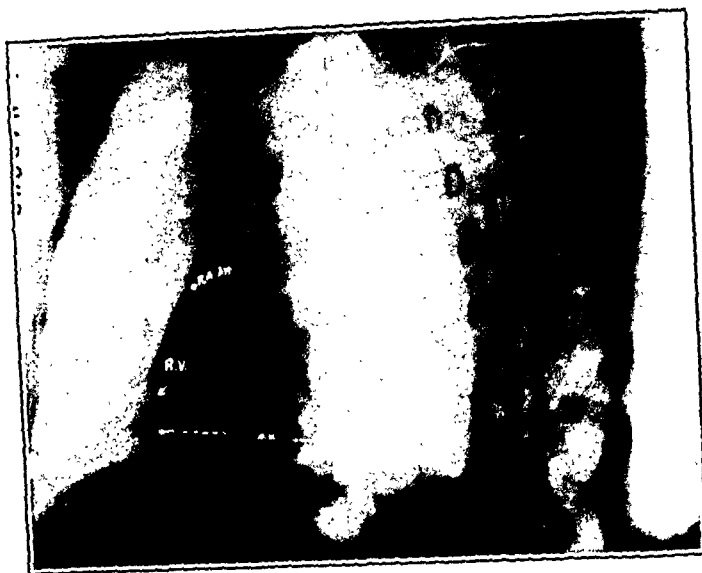


Fig. 1.—Normal heart in left anterior oblique position. In this position a far greater part of the right ventricle can be visualized than in the routine posteroanterior position.

Note the incisura (at arrow) indicating the interventricular groove, forming one terminus of the right ventricle, the other terminus being formed by the lower part of the ventral (outer) border. This part of the right ventricle corresponds approximately to the "inflow tract."

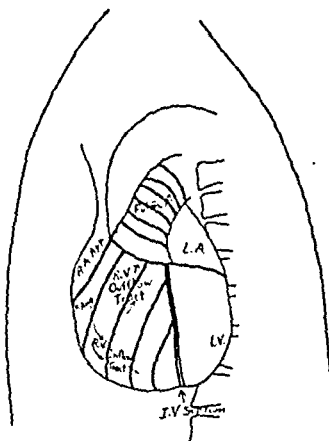


Fig. 2.—Copy of radiograph in left anterior oblique position. The heavy black lines represent metal strips placed around the right ventricle of a cadaver heart in situ. Case of mitral stenosis. Note the extent to which the right ventricle forms the lower and ventral (anterior) borders. The right auricle has been rotated posteriorly and the right auricular appendix forms the upper part of the ventral border. (W. Koch and W. Wieck, *Anatomische Analyse des Roentgenbildschattens des Herzens*.)

On the diaphragmatic surface the differentiation of the parts of the border formed by right and left ventricles can be made only by finding an anatomical landmark which corresponds to the marginal part of the interventricular sulcus.

There have been several attempts to divide the ventricular outline into its right and left components. Bordet's<sup>3</sup> method establishes an apex,

which does not, according to the author's own description, correspond to the terminal portion of the interventricular groove as studied in post-mortem specimens. His established apex is the point lowest and furthest out on the left lower cardiac contour and is found several centimeters from the terminus of the interventricular groove. Only in longitudinal hearts do the two points correspond. In left ventricular enlargement, the points do not coincide, and this apical point is 2 to 3 cm. above and lateral to the interventricular groove.

O'Kane, Andrew and Warren<sup>4</sup> have attempted to reconstruct the course of the interventricular septum in left anterior oblique position, and its termination on the diaphragmatic contour by drawing a perpendicular from a line connecting the upper parts of the two ventricles (the junction of the right ventricle and aorta to the junction of the curves

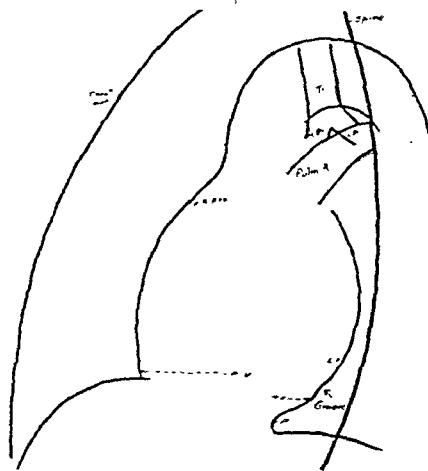


Fig. 3.—Fluoroscopic tracing of a normal heart in left anterior oblique position. Compare with Fig. 2. P indicates one of the points occurring on the diaphragmatic contour which must be differentiated from the groove.

of the left ventricle and left auricle). The point at which this perpendicular transects the diaphragmatic border was considered to be the terminus of the septum.

We have been impressed during routine fluoroscopy in the last three years by the frequency with which an indentation in the left lower contour in the left anterior oblique position has been encountered. This indentation has the appearance of a groove or lip formation and is best seen in deep inspiration and in systole, when this part of the heart is raised from the diaphragm. It was felt that this indentation might mark the interventricular groove at its terminal point. If this contention could be verified, an important landmark would be established, the use of which would reveal the exact participation of the right and left ventricles in forming the diaphragmatic contour. Enlargement of the right ventricle on its lower surface could thus be recognized and the extent of inflow tract involvement could be appreciated (Fig. 3).

METHOD

In order to establish identity of the interventricular groove with the indentation as seen in fluoroscopy, the following steps were taken:

Isolated and unopened human hearts were covered with barium over the lower portions of the interventricular sulcus. The sulcus can be



Fig. 4.—Heart-lung-liver dissection in posterior anterior position. Barium mixture in interventricular groove. Note that in this position the direction of the interventricular groove is vertical.



Fig. 5.—Heart-lung-liver preparation in posterior anterior position.



easily identified by the course of the coronary vessels. The specimen was then radiographed in postero-anterior and left anterior oblique positions. In these positions, the terminus of the interventricular groove appeared in the left lower border of the heart. In left anterior oblique, the groove as represented by the barium line corresponded to that seen in fluoroscopy.



Fig. 6.—Same heart-lung-liver preparation in left anterior oblique position. (Compare with Fig. 5.) The direction of the interventricular sulcus now assumes an oblique course and the base is wide.



Fig. 7.—Heart-lung-liver preparation. Case of right ventricular enlargement, following chronic pulmonary fibrosis. Radiographed in left anterior oblique position with barium mixture in the interventricular groove. Note marked lower width of heart and position of interventricular groove.

To obtain more accurate data comparable to the positions of the organs in life, dissections of the heart-lung-liver-spleen-stomach were removed *in toto* without disturbing the original relationships, and radiographed in postero-anterior and left anterior oblique positions. The barium line, indicative of the interventricular sulcus, could be clearly recognized. In the postero-anterior position its direction was more or less vertical, in left anterior oblique the direction was oblique with shifting of the lower portions to the left. The position of the groove in left anterior oblique corresponds to the position of the incisura as seen in fluoroscopy (Figs. 4, 5, 6).

In cases of right ventricular enlargement the barium line representing the interventricular sulcus had a lateral oblique course (left anterior



Fig. 8.—Photograph of *Situs Thoracis*. Case of rheumatic valvular disease, mitral stenosis predominating. Illustrates: (a) Marked enlargement of the outflow tract indicated by the prominence of the pulmonic conus. (b) Marked enlargement of the inflow tract indicated by arrows. Note the increased width of the lower border of the heart and the displacement of the interventricular groove.

oblique position) with its terminus on the diaphragm definitely displaced to the left and upward (Fig. 7).

These observations indicate that the incisura as seen in fluoroscopy can be definitely interpreted as being caused by the terminal portion of the interventricular groove. The active systolic elevation of the groove accounts for the difference in appearance of the groove in fluoroscopy from that in postmortem specimens.

It is difficult to demonstrate the incisura in films in the left anterior oblique position. This is due to the fact that the incisura is seen in systole while the radiographic exposure time includes portions of both systolic and diastolic phases. It is likely that with synchronization of exposure with ventricular systole the incisura may be demonstrated in

films in a much greater proportion of cases. Fluoroscopic examination is indispensable and in addition is sufficiently accurate to make such complicated procedures unnecessary.

The incisura caused by the terminus of the interventricular groove as seen in systole must be differentiated from other indentations in this part of the cardiac contour. Such breaks in contour presenting a somewhat angular appearance may be caused by:

(1) The junction of the inferior vena cava with that of the lower outline of the heart. This shadow is usually located to the right in a central position (see Fig. 3).

(2) In a few instances, a shadow similar to the one caused by the inferior vena cava, but further to the left, may be observed. This is situated below the definitely visualized incisura and may be due to the pericardial portion of the pericardium.

(3) Another indentation lies between the left ventricle and the left auricle above. This is considerably higher than the incisura, and should cause little difficulty (see Fig. 10).

In general, it may be said that the groove is best visualized in vertical hearts. It is also seen, however, in globular and horizontal hearts in a sufficiently large proportion of cases to make it distinctly worth while to look for it.

In reviewing the literature we found that Pezzi,<sup>5\*</sup> observed this indentation, recorded it orthodiagraphically, attributed it to the interventricular groove and attempted to transfer this point to the orthodiagram in the postero-anterior position. No attempts were made by him to observe or utilize this point in reference to right ventricular enlargement.

Koch and Wieck<sup>2</sup> placed metal strips about the individual chambers of the heart in hardened cadavers and then radiographed the thorax in various positions. The interventricular groove was one of these landmarks made visible. This groove corresponds in location and course to that seen in our specimens (see Fig. 2). The groove in neither instance would correspond to the point obtained in the construction of O'Kane, Andrew and Warren.<sup>4</sup> The advantage of our procedure in localizing the interventricular groove is that this is a direct visualization and renders arbitrary constructions unnecessary.

#### ENLARGEMENT OF THE RIGHT VENTRICLE

*Outflow Tract Enlargement.*—The first demonstrable enlargement of the right ventricle occurs in the outflow tract in a direction upward and to the left. During the next phase there is increase in mass ventrally and further upward. The right ventricle encroaches on the left ventricle below as well as above. With further encroachment of the right ventricle upon the left, rotation of the heart and aorta takes place. The lateral

\*For this reference we are indebted to Dr. H. R. Miller.

parts of the left ventricle are displaced posteriorly bringing the right ventricle forward, upward and to the left (Fig. 9).

The radiographic manifestations of these changes consist essentially of an alteration of the upper and middle parts of the left cardiac border without necessarily any change in the outline of the right cardiac border.



Fig. 9.—Enlargement of the outflow tract. The pulmonic conus is prominent. Note the drop in convexity of the left lower border indicating that the left ventricle is not enlarged in this case. Note also that the heart is not enlarged to the right. Case of mitral stenosis.

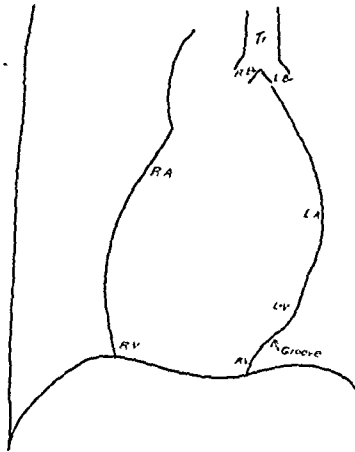


Fig. 10.—Fluoroscopic tracing in left anterior oblique position. Case of mitral stenosis, same as Fig. 9. The interventricular groove is not displaced. The diaphragmatic border is not broadened. Note the indentation between the left auricle and left ventricle.

This absence of enlargement to the right cannot be emphasized too strongly. The varying degrees of this outflow tract enlargement are seen as:

(1) Slight enlargement: increased prominence of the pulmonic artery and conus.

(2). Moderate enlargement: the conus enlargement causes straightening of the normal concavity in the upper part of the left cardiac border (postero-anterior position), prominence of the conus, then actual bulging in this region.

(3) Marked enlargement: still greater enlargement of the outflow tract results in downward prolongation of this bulge or prominence, especially well seen when there is no marked enlargement of the left ventricle (Figs. 9 and 10). (In cases of marked conus enlargement interpretation of the second curve to the left as being due to left auricle has no basis anatomically, except in a few instances when an overlapping of the auricular appendix and the conus may occur.) Enlargement of the



Fig. 11.—Definite enlargement of the outflow tract. The pulmonic conus and pulmonic artery are prominent. There is also some left ventricular enlargement. Heart is not enlarged to the right. The left auricle was not enlarged (autopsy).

outflow tract of the right ventricle, without enlargement of the left auricle or appendix, is sufficient cause to account for all the radiologic changes described above (Fig. 11).

While several of these changes were described in the older radiographic literature, the correlation and interpretation of the above mentioned facts have been definitely established by Assmann<sup>6</sup> and his associates, in whose excellent papers the characteristic radiography and their anatomical bases have been amply correlated. In the American literature, these aspects were recently amplified by Steel.<sup>7</sup>

*Inflow Tract Enlargement.*—Enlargement of the outflow tract is seen chiefly in the left cardiac border; study of that of the inflow tract requires another method of approach. According to Kirch<sup>1</sup> enlargement

of the inflow tract is first manifested by downward elongation of the chamber from the tricuspid ostium to the apex.\* Further enlargement causes additional downward elongation, and broadening of the diaphragmatic surface (Fig. 8). Excessive enlargement of this part of the heart may even displace the right auricle upward and posteriorly to the extent that the right ventricle may actually form a large part of the right lateral border (see Fig. 8), unless there is concomitant excessive enlargement of the right auricle.

To study inflow tract enlargement, we utilize information obtained in the left anterior oblique position. Generally, enlargement of either ventricle will cause an increase in the transverse diameter in this posi-



Fig. 12.—Same case as in Fig. 11. Radiographed in left anterior oblique position. Enlargement of the inflow tract indicated by the prominence of the ventral border of the heart below the angulation. The width of the lower border is increased.

tion. When enlargement of the right ventricle predominates, the increase occurs in the ventral (right) portion (Assmann<sup>6</sup>). The part of the right ventricle responsible for this increase is chiefly the inflow tract (Koch and Wiecek<sup>2</sup>).

The right anterior border in left anterior oblique position consists of the curves of the right ventricle, right auricle and aorta. The enlarged lower and right lateral parts of the right ventricle (inflow tract) will be projected outward causing prominence in the right lower contour. Enlargement of the right auricle influences the upper part of the right border (Vaquez<sup>7</sup>) (see Fig. 2).

The lower curve of the anterior border representing the right ventricle may be rounded or angular. The angulation, when present, corresponds to the greatest amount of bulging of the right ventricle. It is an important landmark and is definite evidence of inflow tract enlargement (Fig. 12). This angulation may, however, disappear when the enlarge-

\*Confirmed by as yet unpublished work of H. Mond, L. Gross and M. A. Kugel (personal communication).

ment of the inflow tract is very marked. It will also disappear when there is enlargement of the right auricle, and the same round contour may result. Certainly it may be said that the portion of the outline below the angulation is right ventricle. Above, it may be either auricle,



Fig. 13.—Advanced enlargement of the outflow tract. Straightening out and prominence of the left upper cardiac border. No enlargement of the heart to the right.

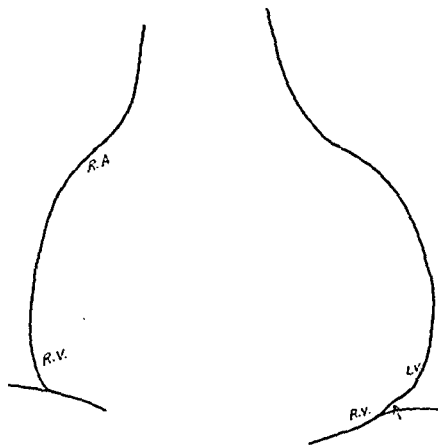


Fig. 14.—Fluoroscopic tracing in left anterior oblique position. Same case as in Fig. 13, marked enlargement of the inflow tract with prominent ventral border, broad lower contour, and displacement of the interventricular groove.

or ventricle and auricle together. It is only in this position (l. ant. oblique) that the right ventricle and right auricle can be differentiated.

The diaphragmatic contour has received little attention, even in the recent literature, chiefly because the differentiation of this outline into

its components is difficult (Assmann<sup>6</sup>). The importance of this much neglected contour has been only recently discussed by Arkussi,<sup>9</sup> who emphasized the significance of right and left ventricular enlargement on the broadening of the base. The localization of the interventricular groove affords differentiation of the diaphragmatic contour into right and left ventricular portions. Enlargement of the diaphragmatic portion of the right ventricle manifests itself (1) in broadening of the base, (2) prominence of the right lower border, (3) and finally, in actual displacement of the groove to the left (Figs. 13 and 14).

There is anatomical evidence of displacement of the septum to the left in right ventricular enlargement (Koch and Wieck<sup>2</sup>). In right ventricular enlargement the septum describes a curve with its convexity to the left. The degree of curvature of the septum in its upper portions does not necessarily correspond to the degree of radiographic displacement of the groove to the left. Inflow tract enlargement may, however, be present without displacement of the marginal portion of the interventricular groove. These observations have been confirmed at post-mortem examinations. It follows, therefore, that the displacement of the groove indicates markedly advanced enlargement of the inflow tract of the right ventricle. With the incisura as a landmark, it was seen that the ratios of portions of the diaphragmatic outline occupied by right ventricle to left ventricle vary from 4 to 1, 5 to 1, or even more, denoting various degrees of right ventricular enlargement. This is contrasted to the 3 to 1 or 2 to 1 ratios observed in the normal left anterior oblique. In right ventricular enlargement the greatest part of the diaphragmatic border as seen in left anterior oblique therefore is contributed by the right ventricle (see Fig. 7).

Enlargement of the left ventricle will tend to displace the septum so that its convexity is to the right. Since the maximal displacement takes place in the upper and not the marginal portions of the septum, it follows that only very marked enlargement of the left ventricle will cause an appreciable displacement of the groove to the right. It seems that enlargement of the inflow tract of the right ventricle displaces the groove more frequently than does enlargement of the left ventricle. This is probably because enlargement of the right ventricle results in rotation of the heart to the left.

In left anterior oblique position the lower ventral border is formed by the right ventricle (the right auricle participating in cases of very excessive enlargement, but not in those of moderate, or even marked enlargement). The diaphragmatic contour up to the incisura is also formed by the right ventricle. Therefore it follows that *an outline representing almost the whole extent of the inflow tract of the right ventricle can be demonstrated radiologically.*

Inasmuch as we have stressed the importance of the groove as a landmark in the differentiation between right and left ventricular contours,



it is necessary to add that there are certain occasions when the incisura cannot be visualized. Such may be the case when the left leaf of the diaphragm is elevated and fixed because of adhesions. Fluid and other shadows also obscure the cardiodiaphragmatic contour. In horizontal hearts with high diaphragm, inspiratory excursions may not be of sufficient depth to reveal the lower segments of the heart. In cases where systolic contractions are superficial and there is no sufficient upward movement with each contraction, the incisura may be suspected but not clearly defined. This is frequently the case when cardiac enlargement is excessive, especially when the left ventricle is so large that the groove is located at or about the center of the diaphragmatic contour of the heart (left anterior oblique position).

Our observations clearly indicate that the segment of the heart resting on the diaphragm in left anterior oblique position consists of the right ventricle. The incisura, when visualized, was found at or near the point where the cardiac contour on the left side rises from the diaphragm. This localization is remarkably constant. While the ventral border may be influenced by excessive enlargement of the right auricle, definite inflow tract enlargement always results in a broadened base extending to the incisura. When the groove is not visualized because of the difficulties mentioned above, we feel that one can assume that the right ventricle reaches to the lower portion of this rising line. This holds true with the exception of those cases where the left ventricle is markedly enlarged on its diaphragmatic surface.

From the above consideration it follows that with the use of the method described, not only is the right ventricular outline defined, but its constituent physiological units are differentiated. To study satisfactorily the right ventricle it is necessary to examine the outflow tract (postero-anterior position), then the inflow tract (left anterior oblique position). Presence of outflow and inflow tract enlargement can so be recorded. It is suggested that this procedure be applied routinely in radiography of the heart, since it gives information not available by any other method.

By applying this method to examination of extensive clinical material we found that enlargement of the outflow tract is easily recognized, even in its early stages, and need not be associated with demonstrable enlargement of the inflow tract. On the other hand, inflow tract enlargement could be definitely shown roentgenologically only when there was considerable enlargement of this portion, and only rarely in the absence of outflow tract enlargement. The cause of the difficulty in recognizing incipient enlargement of the inflow tract lies in the variability of the normal anterior contour in left anterior oblique position. Only considerable deviation from normal will afford positive diagnosis of enlargement.

To evaluate the findings obtained in this study it is necessary to recall the general rule that the object of radiographic examination of the heart is limited at present to recognition of enlargement of individual chambers of the heart. The significance of this enlargement must be reserved for clinical studies to which radiography supplies important data.

#### SUMMARY

A fluoroscopic method for demonstration of the marginal section of the interventricular groove located on the lower anterior surface of the heart is described, and the application of the method is discussed.

A procedure for systematic radiologic study of the outflow tract and of the inflow tract of the right ventricle is described.

Based upon this study the following criteria for recognition of enlargement of the right ventricle are suggested:

(A) Outflow tract (postero-anterior position).

Prominence of the pulmonic artery and conus on the left upper or on the left upper and middle cardiac border.

(B) Inflow tract (left anterior oblique position).

(1) Prominence of the right lower cardiac border, (2) angulation of the anterior contour, (3) broadening of the diaphragmatic outline, (4) displacement of the interventricular groove to the left and upward.

This study was possible through cooperation of Dr. A. J. Bendick. We are greatly indebted to Drs. D. Perla, V. H. Kugell, and S. Rosen for their valuable assistance in carrying out the postmortem studies.

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# FUNCTIONAL LONGITUDINAL BLOCK IN THE HUMAN HEART

## A PROBABLE CASE WITH UNUSUAL ARRHYTHMIA\*

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### INTRODUCTION

THE case with its electrocardiographic record is presented because it represented, we believe, a phenomenon which is in conflict with the present generally accepted opinions regarding the mechanism of the spread of the excitation and contraction waves through the human heart.

A summary of the patient's history is as follows:

### CASE REPORT

Miss A. T., a young woman aged twenty-one years, was first observed in the University of California Hospital on September 12, 1924. Her history was characteristic of exophthalmic goiter for three years, with the usual symptoms of weakness, nervousness, loss of weight, tachycardia, a large vascular goiter and ocular changes. She had been under the care of Doctor J. W. James of Sacramento, California, who had treated her for congestive heart failure and thyroid disease by rest, iodine and roentgen ray therapy (thirteen exposures over the thyroid gland and ten over the thymus). She had had alternating periods of tachycardia and bradycardia.

There was a history of involvement of the heart during an attack of scarlet fever at five years of age. There had been several infections diagnosed as influenza, pneumonia and tonsillitis between the ages of sixteen and twenty years.

Physical examination showed the usual manifestations of severe Graves' disease with all the ocular signs associated with the disease including marked exophthalmos. The thyroid gland was of great size and very vascular.

The venous pressure was increased. The liver was slightly enlarged, but there was no edema of the dependent parts. The heart was greatly enlarged to the left. The action was regular, rate rapid, and there were systolic and diastolic murmurs indicative of involvement of both aortic and mitral valves. The systolic blood pressure was 120 and the diastolic was 40 mm. Hg. The basal metabolic rate was 60 per cent above the theoretical normal. The vital capacity was within normal limits.

Teleroentgenograms showed the heart to be enlarged downward and to the left with a straight left border. The apex was rounded. The shadow of the auricles was increased. There was increased density of the shadows over the base of the right lung, and the central markings of both pulmonary fields were exaggerated. There was no evidence of enlarged thymus.

Dental caries was marked and apical abscesses were numerous. Other examinations were unimportant and are therefore omitted here.

\*From the Department of Medicine, University of California Medical School, San Francisco, California.

Read before the meeting of the Association of American Physicians at Atlantic City, May, 1931.

A diagnosis of Graves' disease of marked degree with coincident infectious valvular heart disease with aortic and mitral valvulitis of long standing was made.

The patient remained in the hospital for forty days and was discharged improved. Treatment consisted of rest, high caloric diet, roentgen ray therapy over the thymic region, the insertion of bare tubes of radium emanation (8.0 m.c.h.) into various parts of the thyroid gland and left in situ, iodine in the form of Lugol's solution by mouth, digitalis and alkalis.

The cardiac rate varied from 90 to 120 per minute, and the rhythm was regular until the fifth week when complete heart block suddenly developed, the auricular rate being 130 and the ventricular rate 55 per minute. For three days thereafter the block persisted, and on the third day the auricular rate was 140 and the ventricular rate had increased to 85 per minute. After each second or third auricular complex in the electrocardiogram, the otherwise independent rhythm of the ventricles was disturbed by a response of these chambers, which seemed to take its time from the auricular impulse which preceded it by 0.20 to 0.28 sec. This auriculo-ventricular block was coincident with overdosage of digitalis and disappeared when the drug was eliminated.

Throughout the period of observation, and before any digitalis was given, the T-waves in Lead III of the electrocardiogram were inverted and there was a moderate degree of right electrical axis deviation.

Upon discharge, the thyroid condition was greatly improved. During the second week of observation the basal metabolic rate had fallen to 44 per cent above the theoretical normal. There was a gain in weight of 6 pounds. With clinical improvement of the Graves' disease it was still more apparent that there was aortic and mitral valvular disease of the heart.

From December, 1924, until February, 1928, the patient pursued a fluctuating course with a gradual trend of improvement in the signs and symptoms of the Graves' disease under oral iodine and roentgen ray therapy. By February, 1927, except for slight dyspnea on moderate exertion and periods of palpitation, she had no symptoms. Signs of aortic and mitral valvulitis were constant. The thyroid gland could not be definitely felt. On one occasion an irregularity of rhythm was noted at examination with apparent coupling of the beats. We were unable to secure an electrocardiogram on this day.

On February 23, 1928, she returned for an electrocardiogram and basal metabolic rate determination. The latter showed 8.8 per cent below the theoretical normal.

The electrocardiogram, taken after a considerable delay which greatly disturbed the patient, was remarkable and is the subject of this report. She was not conscious of having had any attacks of palpitation during that day. Miss Nagle, our technician, observed the irregularity in the movement of the shadow of the fiber after an initial record had been made. Immediately thereafter, Miss Nagle took a second record, the curves of Leads II and III showing the abnormal responses, prior to the termination of the attack. The sequence in taking this record was Lead III, Lead II, and lastly Lead I.

It can be stated with positive assurance that no one else was in the electrocardiographic laboratory except the patient and the technician. Although we have cables to two ward stations, the terminals at the galvanometer are so arranged that these ward stations cannot be connected simultaneously with the laboratory inlets. No one other than the technician had any duties in arranging the electrodes for patients

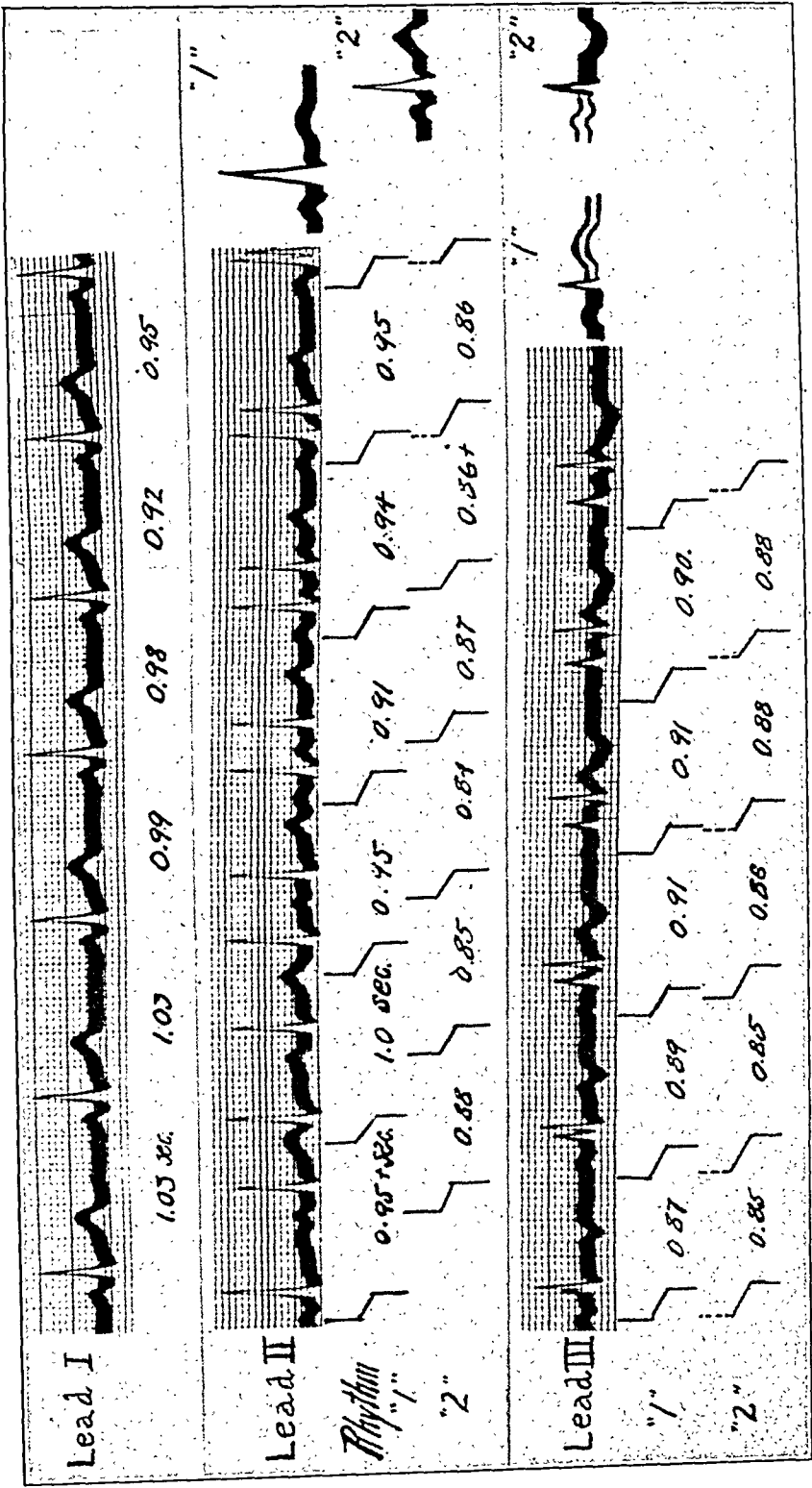


Fig. 1.—Electrocardiogram of Miss A. T. Time interval between beats during the period of arrhythmia indicated in seconds. Freehand tracings of the deflections in the two rhythms indicated by "1" and "2" to the right of Leads II and III. The skeleton portions of these tracings are estimated reconstructions. The vertical lines indicate the positions of the auricular and initial ventricular deflections in each rhythm. No attempt is made to place these lines accurately at the onset of the par-ticular deflections.

at the ward stations or at the central station. The technician could not have been in contact with the body of the patient and have released the plate carrier at the same moment since the couch was several feet removed from the galvanometer. The technician made no direct contact with the galvanometer terminals.

In June, 1928, four months after the unusual curves were obtained all the upper teeth of the patient were removed, and for a month thereafter she had frequent brief attacks of palpitation with great distress and cyanosis. The rate at the apex varied from 30 to 150 per minute as observed by her mother.

We have been unable to observe her in another of these attacks, and interim electrocardiograms have not shown variation in the shape or height of the deflections from the previous records during regular rhythm. The QRS time interval increased from 0.10 to 0.14 sec. in the four years from 1924 to 1928.

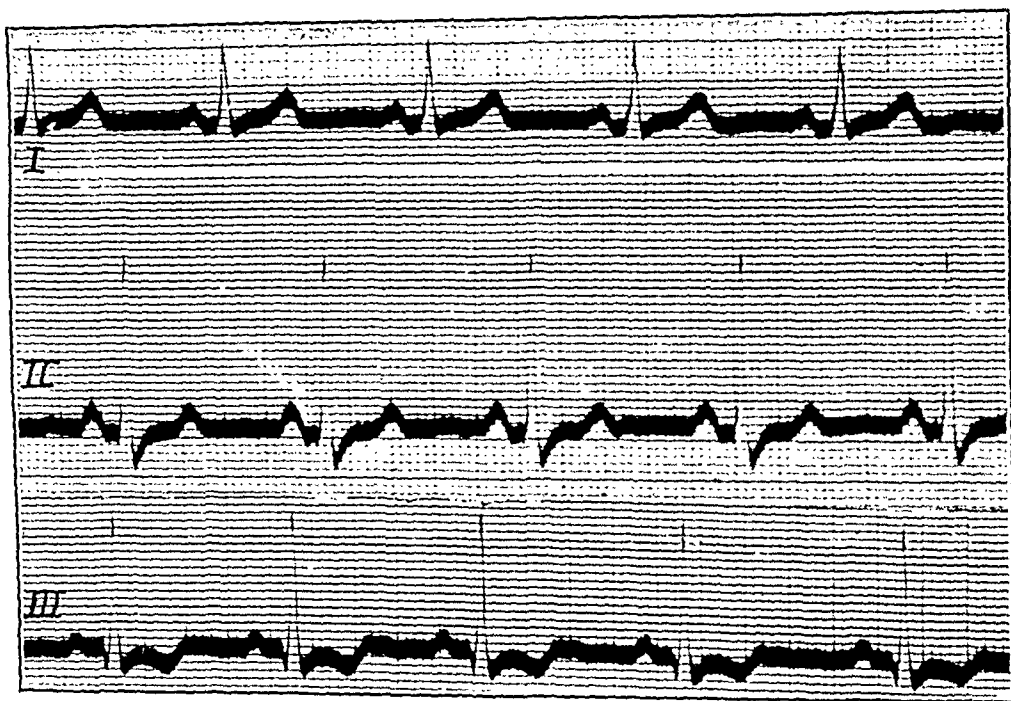


Fig. 2.—The electrocardiogram of Miss A. T. after the period of arrhythmia.

#### DISCUSSION

Fig. 1 is the electrocardiogram taken during the above described attack with an Einthoven string galvanometer, Cambridge Instrument model. The string calibration was 1 centimeter response to 1 millivolt. The patient was on an isolated circuit with no individual in contact with her or with the electrode leads; and it was impossible for the technician using a standard technic for operating the apparatus to superimpose her own cardiogram on that of the patient, as previously detailed.

It will be seen in an analysis of Leads II and III, taken during the attack, that two independent rhythms, regular but of different rates, are present. Both rhythms have normal P, R, S and T-waves, but the forms of each of these waves differ as will be seen from a reconstructed analysis of them in Fig. 1. What may be called rhythm 1 had a rate

of approximately 80, and what may be called rhythm 2 had a rate of approximately 85 per minute. The P-R intervals of both rhythms are 0.17 sec., as closely as can be measured. It will be observed that there is nearly, although not precisely, the same cyclical variation in both rhythms suggesting the same autonomic nervous system control of both pacemakers.

The patient's normal electrocardiogram, taken on the same day and repeated many times without appreciable alteration in form, is given in Fig. 2, and it will be seen that the P, R, S and T-waves in both Leads II and III are electrical summations of the potentials demonstrated by the individual rhythms during the attack in Leads II and III of the electrocardiogram in Fig. 1. It is believed that this is genuine proof that this remarkable double rhythm was not an artefact.

There is no experimental proof at hand to lead us to draw any certain explanation for this phenomenon if the two auricular and ventricular

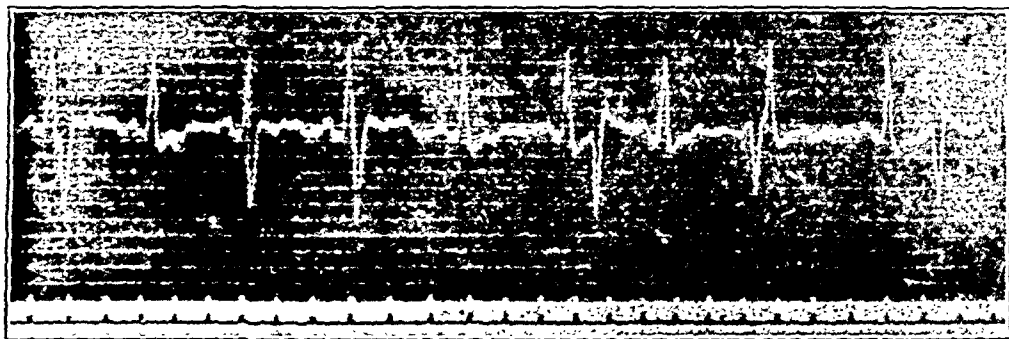


Fig. 3.—Human electrocardiogram from Hoffman which he interpreted as an illustration of longitudinal dissociation.

contractions occur simultaneously and are so completely isolated from each other that there is no influence of one rhythm on the other. If one contraction wave invaded the area of the second wave, the normal refractory quality of the heart muscle, which is presumably present, would prevent a second contraction occurring. On the contrary the second cycle of auricular and ventricular deflections occurs unimpeded during all phases of the cycle of the first rhythm.

An hypothesis may be ventured, namely, that a portion of one or both auricles is responding to a constant pacemaker, independent of the normal pacemaker, with a pathway to one or both ventricles, and, that one or both auricles and ventricles, and the pathway between, are dissociated by all functional contact from the remainder of the heart. It is as if longitudinal sections of the heart were acting independently. Such a phenomenon has been termed longitudinal dissociation but only reported in isolated beats (Hoffman<sup>1</sup>) (Fig. 3\*).

\*This record has been examined by many cardiologists, and it is uniformly agreed that the possibility of artefact cannot be excluded.

It is not necessary to assume that the dissociation is a true hemisystole phenomenon; nor, if it were such, is there any known proof in man that the auricular or ventricular deflections must be in opposite directions in the independent rhythms?

The unconfirmed work of Kent,<sup>2</sup> published in 1893, illustrated both anatomical and functional pathways between the auricles and the ventricles apart from the normal sino-auricular and auriculoventricular nodes. The work was done on mammalian hearts and has not been adequately checked by repetition. It is conceivable that in the develop-

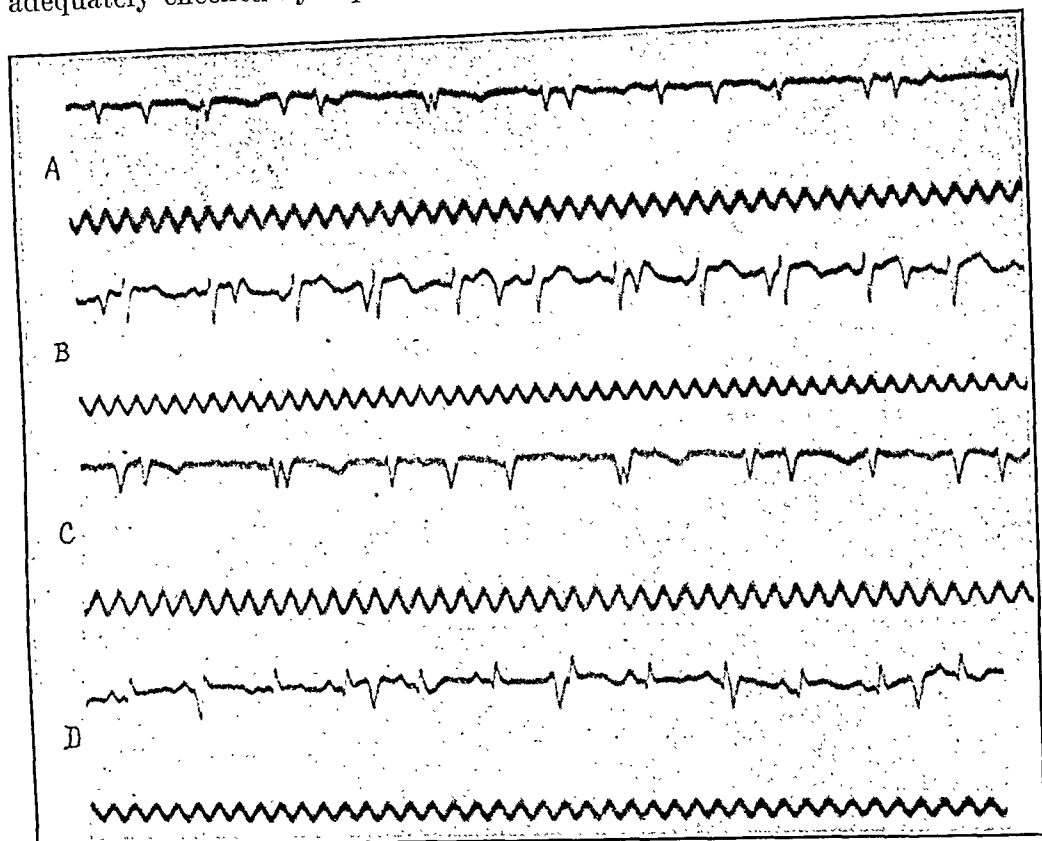


Fig. 4 A, B, C, and D.—Four electrocardiograms of newborn infants. (From Burgard and Wunnerlich.)

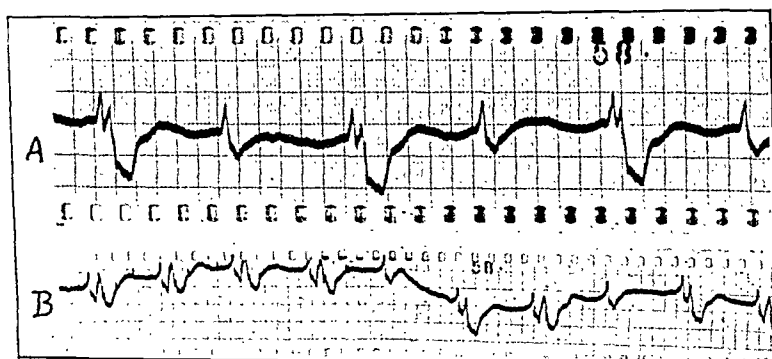


Fig. 5 A and B.—Electrocardiogram from 90-hour chick embryo. Direct axial leads. Two portions of the same continuous record.

ment of the human heart such a mechanism may be present, through faulty differentiation in the conduction system, after the division of the heart from a two to a three and from a three to a four chambered organ. This faulty differentiation may persist as a functionless anatomical structure in certain hearts with rare periods of reversion of such



a pathway to activity. Only by a fortunate accident could this reversion be recorded. Certain pathological changes may also predispose to this mechanism.

It occurred to us that other evidence of such a pathway could be found in the embryonic heart or in the heart of early infancy. Fig. 4A, B, C and D are the electrocardiograms obtained from premature infants by Burghard and Wunnerlich<sup>3</sup> who interpreted the irregularities as recurrent extrasystoles. These records, we believe, illustrate similar dissociation within the ventricles. It is not possible from the curves presented by these authors to determine whether definite auricular waves precede the ventricular deflections.

Fig. 5 illustrates the records that were taken with an amplifying type of galvanometer on one of a series of chick embryos. This particular record was made from a specimen of an approximate age of ninety hours. Here again no auricular waves were recorded, but the heart was grossly observed to contract segmentally along a longitudinal plane. The electrocardiographic record, taken from axial leads, showed apparently the same functional dissociation with evidence that the second portion of the heart was uninfluenced by the refractory period of the contraction waves of the first portion.

#### CONCLUSION

Whereas it is recognized that no conclusive explanation can be given for the phenomenon observed in this patient, and that the possibility of artefact cannot be completely excluded, we feel that it represents an unusual state of intracardiac dissociation and possibly may be a reversion to an embryonic mechanism.

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# THE STATUS ANGINOSUS INDUCED BY PAROXYSMAL AURICULAR FIBRILLATION AND PAROXYSMAL TACHYCARDIA\*

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WILLIAM HEBERDEN<sup>1</sup> in 1768 was the first to give the name "angina pectoris" to the syndrome of paroxysmal substernal oppression on exertion. A great deal has been written about this syndrome since that time, and we have not yet learned the whole story. We have known for years that more factors than one have a part in the production of angina pectoris and only this year Lewis<sup>9</sup> has attempted to separate off one group of cases from the rest, that group consisting of patients with marked hypertension and tachycardia occurring only at the time of the angina pectoris and attributed by him to a kind of vasoconstrictor storm in which the coronary arteries are among the vessels involved. In the present paper we wish to call attention to still another association of angina pectoris, namely that with various types of paroxysmal tachycardia.

It is a fact generally known that sino-auricular tachycardia and a rise in blood pressure frequently occur during an attack of angina pectoris or may bring on an attack. Mackenzie<sup>10</sup> calls particular attention to this, citing a case in which during a test for sensitiveness of the skin of the left breast the heart rate suddenly increased from 90 to 130 with an accompanying severe attack of angina pectoris. Numerous other authors, particularly Lewis<sup>9</sup> during the past year, have written of the increase in blood pressure and also of sino-auricular tachycardia with angina pectoris.

Occasionally angina pectoris and paroxysmal auricular fibrillation or flutter or paroxysmal tachycardia occur in the same patient at different times. Levine<sup>7</sup> found that only one out of 103 cases of angina pectoris showed persistent auricular fibrillation and that one patient showed transient fibrillation; during this same period he saw 423 cases of persistent auricular fibrillation and of this group 200 were observed in elderly persons with "chronic (nonrheumatic) myocarditis." Mackenzie,<sup>10</sup> Lewis,<sup>8</sup> and White<sup>12</sup> have also called attention to the infrequent association of angina pectoris and auricular fibrillation. It is a common clinical finding that when persistent auricular fibrillation sets in angina pectoris usually disappears. However, paroxysmal auricular fibrillation is not so rare in patients with angina pectoris.

Infrequently, paroxysmal auricular fibrillation or paroxysmal tachycardia is found complicating acute coronary occlusion. This fact has

\*Presented by title at the Annual Meeting of the Association of American Physicians, Atlantic City, May, 1931.

been noted by various writers; for example, Robinson and Herrmann<sup>11</sup> reported that of four cases of paroxysmal ventricular tachycardia, one had coronary thrombosis (proved at postmortem examination).

Frequently, discomfort occurs with paroxysmal auricular fibrillation, paroxysmal auricular flutter, or paroxysmal tachycardia, but such discomfort is not generally of the nature of angina pectoris. Lewis,<sup>8</sup> in his discussion of the symptoms of paroxysmal tachycardia, included in one group of such cases "anginal symptoms, varying in intensity from slight precordial pain or a sense of compression with skin tenderness to the violent continuous pain radiating in the characteristic fashion over the chest into the neck, into the left arm, or both arms, and into the abdomen." Barnes and Willius<sup>2</sup> reported 19 cases of paroxysmal tachycardia with pain similar in type and location to that seen in angina pectoris but of longer duration, the pain occurring only with the paroxysms of tachycardia. The patients did not have angina pectoris between the paroxysms. Laslett,<sup>6</sup> among others, has noted pain occurring during paroxysmal auricular fibrillation, but not characteristically anginal.

Finally, *angina pectoris is induced in rare cases as a status anginosus by paroxysmal auricular fibrillation, paroxysmal auricular flutter, or paroxysmal tachycardia in patients who already have shown angina pectoris on effort.* It is the purpose of this report to call attention to this combination which, though rare, is of considerable importance, particularly because of the need of differentiating it from coronary thrombosis.

Three of the four case reports recorded herewith illustrating this condition were obtained from the records of 4,000 cardiac patients seen in our private practice. For the remaining case report we are indebted to Dr. Frank M. Howes of New Bedford, Mass. We have searched the records at the Massachusetts General Hospital without being able to find a clear-cut case of this syndrome. There were several doubtful cases.

#### CASE REPORTS

CASE 1.—*Angina pectoris and paroxysmal auricular fibrillation.* W. P. B., a married woman of sixty-eight years, was seen on August 3, 1930, by Dr. Howes.

The essential points in her past history were that there had been no illness except colds, and no pregnancies. For the past three or four years she had had pain under the sternum on exertion, with distress radiating down both arms.

On August 3, 1930, while quiet at home, she complained of pain in the chest, substernal in location and radiating down both arms. This pain felt exactly like her angina pectoris of effort but it occurred while she was quiet and persisted for hours. Dr. Howes was summoned and administered morphine subcutaneously. He thought at the moment that he was dealing with acute coronary thrombosis but later events caused him to change his mind.

Physical examination at this time (August 3, 1930) revealed a well-developed, slightly obese woman. Her color was good and the pupils were normal. The teeth were false except for six in the lower jaw in front. A small adenoma of

the thyroid was felt. The heart borders could not be made out. There was a blowing apical systolic murmur replacing the first sound, and a rough systolic murmur was heard in the aortic area also. The rhythm of the heart was absolutely irregular at a rate of 120 beats per minute. The systolic blood pressure was 140 mm. of mercury. There was no edema of the lungs or extremities.

The auricular fibrillation stopped while the patient was being examined and the pain went away at once. The rhythm was then regular at a rate of 68 beats per minute. There were no sequelae even suggesting coronary thrombosis.

The patient was digitalized and then given a ration of one and one-half grains of digitalis five days per week. She has continued to have definite angina pectoris associated with exertion. The blood pressure has varied from 160 to 194 mm. of mercury systolic and from 80 to 88 mm. diastolic. The pulse has remained regular at a rate of 68 to 70 beats per minute, except during paroxysms of fibrillation. She has had three such attacks lasting for one to three hours and each attack has been accompanied by angina pectoris.

CASE 2.—*Angina pectoris and paroxysmal auricular fibrillation.* C. R. S., male, aged sixty-two years at the time of his first attack of paroxysmal auricular fibrillation with angina pectoris in December, 1929, was seen by us in consultation for the first time on January 17, 1928. He had always been well and active, except for occasional attacks of gout and an appendectomy in 1892, until 1908 when he first began to feel on exertion, such as golfing uphill, low substernal distress and pain, radiating upwards and outwards part way to the axillae, more on the left. When the oppression was more severe he would notice, in addition, aching in both wrists, but not in the arms or hands. This pain would last five to ten minutes and would disappear on resting. At that time the pain did not interfere with his work or play, but there was a gradual increase in the frequency of attacks and to some extent an increase in severity of the attacks. During the two years prior to consultation he had been greatly crippled by the angina pectoris and had led a retired, sheltered, and inactive life. The attacks might occur several times in twenty-four hours. As he was very sensitive to nitroglycerine he did not use it much but said that he found aspirin somewhat helpful.

On physical examination he was found to be well developed and nourished. His pupils were equal and active. The lungs were clear. The liver was not felt. There was no edema of the extremities. The maximal apex impulse of the heart was felt under the sixth rib, 9.5 cm. to the left of the midsternal line and 1 cm. beyond the midclavicular line; the left border of dullness corresponded. There was a moderate blowing aortic systolic murmur, heard less well at the apex. The rhythm was regular and the pulse and apex rates were 72 per minute. The blood pressure was 170 mm. mercury systolic and 70 mm. diastolic. The electrocardiogram showed normal rhythm, at a rate of 80, moderate left axis deviation, and rather wide S-waves in Lead II.

He was seen again by us on September 14, 1928, and stated that his angina pectoris had continued more or less the same until about one month prior to this visit when it began to get much worse and he had had daily attacks. He found he could take nitroglycerine grains  $1/200$  and this dose gave quick relief. Physical examination and electrocardiogram were essentially as before.

He was next seen by us at his club on December 21, 1930, at which time he was in the midst of a paroxysm of auricular fibrillation, the ventricular rate being 120 to 150. He had severe precordial and substernal pain which had at once required  $1/8$  grain of morphine sulphate subcutaneously, then  $1/4$  grain more just before we saw him, and finally  $1/6$  grain in addition one-half hour later. The paroxysm had begun after dinner and was quickly attended by the pain. Nitrites gave no relief. He was taken to the hospital where the palpita-

tion (a relatively slight symptom) and the pain (severe) continued, although numbed by the morphine, until four-thirty the following morning (a total of eight and one-half hours). He slept the remainder of the night. When seen in the morning his pulse was regular at 80; he looked well and was free from pain. An electrocardiogram taken that same day showed normal rhythm, at a rate of 75, with marked left axis deviation.

He admitted at this time (December, 1930) that during the previous year he had had angina pectoris daily, and that there had also occurred, mostly after dinner in the evening, or later at night, spells of auricular fibrillation once or twice a week, attended by persistent pain and lasting a few hours.

He was seen again in his rooms on the afternoon of April 2, 1931. At 8:30 A.M. there had begun his first attack of absolute arrhythmia (with great pain) since the previous November. He had been given morphine sulphate 1/4 grain subcutaneously at noon and had gotten relief from this in two hours. At 3:15 P.M. the heart was absolutely irregular at a rate of 130. At 8:30 P.M. he felt much better, was without pain, and the pulse was regular at 66.

He quickly recovered from this attack, returned to his usual state of health, but died suddenly on June 16, 1931.

CASE 3.—*Angina pectoris and paroxysmal auricular fibrillation.* E. de C., female, aged seventy-five years, was first seen by us as a private patient on December 29, 1930. She said that she had been always well and active but nervously sensitive. For the past year she had noticed substernal oppression on exertion, especially on hurrying or on walking uphill, which oppression had been quickly relieved by rest or nitroglycerine which she had used a few times. She had had some dyspnea on exertion for the year prior to consultation.

About eight or nine months prior to this visit she had had a spell of rapid, irregular palpitation with severe anterior chest pain lasting several hours. She had a second similar spell two or three months after the first.

On December 19, 1930, during dinner and after an unusually active day, she was seized by severe pain under the right scapula radiating down the right arm and lasting for one and one-half hours unchanged, and less severely for several hours after that. She did not notice any palpitation at first but when Dr. James Faulkner saw her an hour after the onset of the attack, he found a rapid irregular heart rate (auricular fibrillation). The blood pressure at this time was 135 mm. mercury systolic and 90 mm. diastolic. The lungs showed moist râles at both bases. There was little or no cyanosis. Pantopon, gr. 1/3, and digitalis, 0.7 gram, were given and the next day the heart rate had dropped to 108 but was still absolutely irregular. Normal rhythm returned spontaneously about thirty-six hours after the onset of the attack. There was no fever after this attack or other evidence of coronary thrombosis.

On physical examination in our office on December 29, 1930, she appeared but slightly ill. Her color was fair and she was breathing normally. There was no engorgement of the cervical veins. Her heart was enlarged, the sounds were of good quality, and there were loud apical and moderate basal systolic murmurs. The rhythm was normal and the rate was 84 per minute. The blood pressure was 200 mm. of mercury systolic and 90 mm. diastolic. The electrocardiogram showed auricular premature beats at a heart rate of 105, and bundle-branch block.

It was reported by letter from Florida on April 1, 1931, that she had done very well until two to three weeks prior to that date when jaundice began. As this did not clear up she was operated on and two gallstones were removed. Her condition was more or less critical for a few weeks but she recovered and returned north.

On May 14, 1931, she was found dead in bed in the morning.

CASE 4.—*Angina pectoris and paroxysmal tachycardia.* W. E. C., male, aged sixty-six years, was seen in consultation by us on July 24, 1930. His past history was irrelevant. His present illness started a few years before his visit to us when he began to notice slight high substernal oppression on considerable exertion such as walking fast up a hill. This would last only a few minutes and there was no radiation. Early in May, 1930, he first began to have spells of weakness. The first two came on after breakfast about two weeks apart and lasted ten to fifteen minutes, passing off with rest.

On May 25, 1930, while at work in his drug store he was suddenly seized by a cold sweat and weakness. He had to sit down and in a few minutes he experienced substernal pain radiating to the left shoulder and down the left arm to the wrist. He was taken home and given morphine sulphate subcutaneously. The pain lasted an hour or more. He remained in bed one and one-half days; there was no fever. He then resumed work but that night he had a very mild brief attack of precordial burning. He then felt all right for over a month but he spent three weeks in bed.

On July 19, 1930, after having been out riding in the afternoon he was suddenly seized, while brushing his teeth, by a spell of racing of his heart followed in five minutes by severe substernal and left arm pain requiring three-eighths of a grain of morphine sulphate subcutaneously. Physical examination that night by Dr. John Sproull revealed a well-developed and nourished man lying flat in bed without cyanosis. He was in a cold sweat. There were rapid pulsations of the veins of the neck. The heart rate on repeated counts was 196 per minute, and the sounds were tic tac in character, but the rhythm was regular. The blood pressure was 120 mm. mercury systolic and 100 mm. diastolic. The rate continued the same for four hours after the administration of morphine but the pain gradually went away in an hour or so under the influence of the drug. The next day he felt all right and continued to feel well although he rested in bed until the day of his office visit to us (July 24, 1930).

On this date his physical examination revealed frequent premature beats, a pulse rate of 80, no evidence of congestive failure, good heart sounds, and heart about normal in size. There were no murmurs. The blood pressure was 120 mm. mercury systolic and 80 mm. diastolic. Fluoroscopic examination showed a normal heart with considerable tortuosity of the aorta. The electrocardiogram showed ventricular premature beats at a rate of 95 with intraventricular block.

A diagnosis of coronary disease with aortic sclerosis, paroxysmal tachycardia, angina pectoris, and intraventricular block was made.

#### SUMMARY OF CASE REPORTS

Case 1: Definite attacks of angina pectoris on effort, free of tachycardia, during four years prior to consultation. Observed during an attack of status anginosus brought about by paroxysmal auricular fibrillation and disappearing immediately upon cessation of the paroxysm of auricular fibrillation.

Case 2: Definite angina pectoris on effort for twenty-three years. During the last eighteen months of his life he had several attacks of status anginosus brought on by paroxysmal auricular fibrillation; between the attacks of status anginosus he had the usual attacks of angina pectoris on effort.

Case 3: Angina pectoris on effort for about one and one-half years before death. During the last fifteen months of her life she had

three attacks of status anginosus brought on by paroxysmal auricular fibrillation.

Case 4: History of angina pectoris on effort for several years. During the month prior to consultation he had two attacks of status anginosus brought on by paroxysmal tachycardia.

#### DISCUSSION

Angina pectoris induced as a status anginosus by paroxysmal auricular fibrillation or paroxysmal tachycardia, although rare, should be recognized and differentiated from other conditions, in particular, coronary thrombosis. The points in favor of the diagnosis are as follows: a history of previous angina pectoris, of previous paroxysmal tachycardia or paroxysmal auricular fibrillation, and of their association; the finding of a very rapid heart rate on physical examination at the time of the pain; the demonstration of auricular fibrillation, auricular flutter, or paroxysmal tachycardia by electrocardiogram in patients during the attack of substernal oppression; and finally, the absence of any evidence of coronary thrombosis after the subsidence of the paroxysm of rapid heart action. The course of the illness settles the diagnosis, but at the onset one must in some cases at least remain in doubt. Nitroglycerine is ineffective and morphine subcutaneously is necessary in either case. Quinidine sulphate may shorten the duration of the abnormal rhythm.

Barcroft, Boek, and Roughton<sup>1</sup> made detailed observations on the circulation and respiration in a case of paroxysmal tachycardia. They found that during attacks the systolic blood pressure fell from 120 mm. of mercury to 100, whereas the diastolic rose from 68 to 80 mm.; the minute volume sank from 5 — 6.1 liters to 2.8 — 2.1 liters per minute; ischemia was noted particularly in the skin as shown by analysis of blood from the basilic vein; the systolic output dropped from 77.5 c.c. to 12.9 c.c. They found no reduction in the oxygen saturation of the arterial blood, but rather a rise.

Carter and Stewart<sup>2</sup> studied a similar case and it is interesting to note that during the paroxysmal tachycardia they found a marked decrease in the arterial oxygen saturation without demonstrable pulmonary congestion to account for it. They also noted a very low oxygen saturation of the venous blood, largely due to stagnant anoxemia, the result of slowing of the circulation.

When a paroxysm of tachycardia starts, a vicious circle is soon set up, because, the heart rate being increased, there is a greater demand for blood to supply the overworking cardiac muscle; however, the faster the rate, the less the minute volume and systolic output, and hence the greater the decrease in blood supply to the myocardium. Thus it seems quite reasonable, if we accept the theory that myocardial ischemia is a cause for angina pectoris, to account in this way for the induction of the status anginosus by a paroxysm of tachycardia or of auricular fibril-

lation, especially in a myocardium whose coronary circulation is evidently already defective as indicated by the clinical syndrome of angina pectoris on effort.

The ultimate prognosis is apparently as grave in the patient with angina pectoris induced by paroxysmal auricular fibrillation or tachycardia as in the patient with coronary thrombosis, for if there is so much coronary narrowing that an increased heart rate alone (without effort) can induce the pain, life is not apt to be long. Two of the four patients we have reported here died suddenly within two years of the time of onset of their paroxysms of angina pectoris induced by spells of abnormal rapid heart action.

#### SUMMARY

We have reported here four unusual but important cases to illustrate the fact that a status anginosus may occur without coronary thrombosis.

A great increase in heart rate due to paroxysmal auricular fibrillation or paroxysmal tachycardia (with accompanying drop in systolic blood pressure or pulse pressure) was evidently responsible for the induction of the angina pectoris that was at other times a characteristic result of effort in all of these four cases. Two of the patients were men, aged sixty-two and sixty-six years, and two were women, aged sixty-eight and seventy-five years. One of the men (the first) and one of the women (the second) died suddenly eighteen months and fifteen months, respectively, after the first attack of angina pectoris induced by the abnormal heart rhythm. The other two patients were alive one year after their first attacks of this nature.

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# TREATMENT OF SPASMODIC VASCULAR DISEASE OF THE EXTREMITIES OF THE RAYNAUD TYPE\*

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IN the course of investigations on thromboangiitis obliterans, arterio-sclerosis, and related diseases, there have come to our attention a number of cases of peripheral vascular disease which do not conform with the well-known types. These cases seem to resemble mild or borderline forms of Raynaud's disease, presenting such symptoms as acrocyanosis, acroasphyxia, numbness, pain or burning of the fingers or toes. The symptomatology, or rather the emphasis of these symptoms, varied considerably among the cases, but they all had one feature in common, a definite relationship between the onset of symptoms and exposure to cold.

Although none of the four cases described below was of the severity originally noted by Raynaud<sup>1</sup> as characteristic for this disease, they represent at least that variety (described by Lewis) characterized by hypersensitiveness to cold resulting in arterial spasm. They show no permanent, irreversible changes such as gangrene or spontaneous amputation, which probably indicates that spasm formed the essential basis of their symptomatology.

These cases have all been treated by a high calcium regime, and they have all improved. Full histories in these case reports are not here given, since the patients presented no abnormalities other than those noted below.

## CASE REPORTS

CASE 1. Mrs. F. H., thirty-two years old, complained for twelve years of coldness and pallor of the fingers of both hands on exposure to cold. For two years, since a thyroidectomy, her condition had been growing steadily worse. Before the beginning of treatment she found that any exposure to cold (going out of doors in cool or cold weather, even with heavy gloves on) resulted in a complete blanching of her fingers, from the tips to the palm, with a numbness and discomfort subjectively, and an extreme coldness of the fingers objectively. After withdrawal from the cold, this stage was followed by a hyperemic red (not cyanotic) stage, which was not painful. Between attacks the appearance of the fingers was normal. Both radial pulses were normal.

After a high calcium regime given by mouth the condition improved, so that the patient never had more than one very mild attack in any single day, no matter how often she was exposed to cold. This mild attack would consist in a blanching of the distal phalanx of one finger only, instead of all the fingers of both hands, as formerly. On intravenous calcium therapy the mild attacks occurred rarely, and there were no severe ones. The appearance of her fingers remained normal when unexposed to cold.

CASE 2. Mrs. M. P., fifty years old, was troubled for two months with attacks of marked burning and blueness of the hands on exposure to cold air. At the onset she had an attack whenever she gripped anything with her hands; later she

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found herself unable to place her hands in cold water without a troublesome sensation of burning, and shortly before beginning treatment she had blueness and burning of her hands on exposure to the outside air.

After one week on the regime she had no more blueness of the fingers, and the burning was markedly diminished. She has had no recurrence now for more than one year, and she has been on medication constantly during that period.

CASE 3. Mr. T. P., twenty-five years old, had been suffering for seven years with dull aching pains in the feet and hands in cold weather. The onset was gradual. There was no history of freezing or other trauma. The condition had been growing steadily worse, so that even moderately cool weather induced the pain. There were no swellings or color changes, but there was markedly local sweating in both hands and feet. The pain was relieved by soaking the painful limbs in hot water.

Treatment was begun in September, 1930, while the weather was still mild and there was no pain. Subsequently, although the excessive sweating has remained unchanged, the patient has been without pain even in very cold weather except for one day when he had pain in his feet while standing outside in the cold during the entire day.

CASE 4. Mr. C. L., thirty-two years old, complained of pain and redness of his hands and feet in cold weather, together with marked itching and sweating. There was no history of trauma.

He improved on dosage smaller than that which we now use, as our present regime had not yet been established. In the course of a month (in February) he reported that his feet were warm, his hands less red, and that the troublesome itching had stopped. When he discontinued treatment for a month, he had a recurrence of symptoms, which disappeared on the resumption of the high calcium schedule.

#### THERAPY

The therapy consists of a high calcium regime which, in order to be adequate, must take into account the various factors concerned with absorption, such as differences among individuals in the absorptive power for calcium, the addition of vitamins, the time of calcium administration, etc. It is our intention to give in a subsequent communication a full consideration of this question; accordingly we shall here confine ourselves to presenting the following schedule of our procedure in these cases.

For two weeks: A daily diet of milk, 1 quart; viosterol, 30 drops; tomato juice, 16 oz.; orange juice, 8 oz.; and lactose,  $\frac{1}{2}$  oz.

The viosterol may be taken in three doses of 10 drops each, or in two doses of 15 drops each.

The tomato juice is given for its high vitamin content, primarily for vitamin B, which favorably affects intestinal tonicity.<sup>2</sup> If tomato juice is not well tolerated, other substances rich in vitamin B may be substituted.

The next two weeks: If results are not satisfactory, calcium salts are substituted for the milk. Either calcium lactate or calcium gluconate may be used.

Dosage of calcium lactate: 80 grains daily in two doses of 40 grains each, 40 grains one hour before breakfast and 40 grains four hours after supper. If the second dose interferes with bedtime, it may be taken four hours after luncheon, and supper should then not be eaten within less than one hour after taking the dose.

Dosage of calcium gluconate: 150 to 180 grains daily, as either a powder or a tablet, plain or effervescent, the time of administration being the same as for the lactate.

The time of administration of the calcium salts is very important, and only small amounts of water should be taken with the tablets. It has been shown that calcium is absorbed best in the interdigestive period<sup>3</sup> and that when calcium is taken "three times a day after meals," as it is so frequently prescribed, a minimum absorption results and the therapy usually fails.

The next week: If there has been no improvement, calcium gluconate administered intramuscularly is added to the treatment. The dosage is 1 ampule (10 c.c. of a 10 per cent solution) daily, with or without parathormone, 20 units (1.0 c.c.).

The next week: If this has not been satisfactory, calcium gluconate or calcium chloride is given intravenously. The dosage is 1 ampule (10 c.c. of a 10 per cent solution) daily.

#### LITERATURE

The recent literature concerning Raynaud's disease makes little definite mention of calcium as a therapeutic agent, notwithstanding repeated references to it in the older literature.<sup>4</sup> Osler, for example, in his textbook,<sup>5</sup> lists calcium lactate, gr. xv three or four times daily, as being very effectual in some cases. Calcium is included briefly by Mumford<sup>6</sup> and by Claude and Tinel<sup>7</sup> in describing treatment in their cases. Neither Poulton<sup>8</sup> in 1926, nor Deschamps<sup>9</sup> in 1929, in reviews of the literature on Raynaud's disease with extensive bibliography, considers calcium. Barath<sup>10</sup> mentions calcium briefly, saying that it has been used by many with little success in angiospastic conditions. Margolin<sup>11</sup> in 1926, described Raynaud's disease occurring in a case of tetany, with the cure of both diseases by the administration of calcium.

In related conditions, such as erythema pernio and acrocyanosis, calcium has been used for many years.<sup>12</sup>

#### THEORETICAL

The explanation for the results obtained in our cases of vasomotor spasm by the use of a high intake of calcium is not entirely clear. Possibly the action of calcium upon this type of vascular spasm caused by cold is analogous or even related to its action in certain so-called allergic conditions characterized by spasm, e. g., bronchial asthma, in which favorable results are often obtained. The analogy becomes even more striking from a consideration of the observations of Thomas Lewis,<sup>13</sup> in cases of Raynaud's disease, that apparently there exists in these subjects a true specific idiosyncrasy or hypersensitiveness to cold which manifests itself through the spasmodic arrest of circulation in the affected parts, independently of the vasomotor nerves.

On the evidence presented by Lewis it seems warranted to question the old idea that the disease is one of the nervous system, and particularly related to the sympathetic nervous system. The newer conception is well summarized by Blackader,<sup>14</sup> who says: "The abnormal element in the syndrome would appear to be a local direct reaction to a lowered temperature, due to a peculiar hypersensibility of the vessel wall, and not the result of a reflex through the vasomotor nerve. . . . The pathological element in the vascular spasm is not of central nervous origin as it has generally been thought to be, and there would appear

to be no foundation for relating this vascular phenomenon with diseases of the nervous system in other portions of the body. Recent research points to the possibility of its being due to some deficiency of calcium in the blood."

In considering "calcium in the blood" it should be understood that the total calcium of the blood serum may be a poor indicator of the calcium activity in the body unless it is very high or very low. For example, in long continued hyperparathyroidism, both clinical and experimental, the serum calcium may drop from its initial elevation into the normal range, while the abnormal drain of the body's calcium stores persists as before.<sup>15</sup> In hyperthyroidism, where there is a large negative calcium balance over long periods of time,<sup>16</sup> the serum calcium seldom gives indication of the calcium loss. The reverse of this situation may be exemplified in those occasional cases of tetany with normal serum calcium level, in which, despite the "normal" blood figure, the symptoms may be ascribed to physiological lack of calcium.<sup>17</sup> Since calcium may be found in the blood in three forms (nondiffusible, diffusible ionic, and diffusible nonionic), it is evidently possible for a total concentration to be within normal limits, while an imbalance among these three forms underlies a physiological disturbance. Our methods of precision are not yet adequate in measuring these forms of calcium.

Percival and Stewart<sup>18</sup> investigated the blood calcium in twelve cases of chronic erythema of the legs resembling erythema pernio or mild forms of Raynaud's disease, and found values ranging from 9.2 mg. to 11.8 mg. per 100 c.c. of serum. In two cases they found 73 per cent and 80 per cent diffusible calcium (by collodion filtration). They administered parathyroid by mouth with no improvement, although the serum calcium rose from 9.2 to 10.6, and from 10.0 to 10.3 respectively (obviously not a significant rise). They conclude that hypocalcemia is not an etiological factor in the disease, nor is calcium effective as a therapeutic agent. They made similar studies in other skin diseases,<sup>19</sup> such as Bazin's disease, chronic leg ulcers, psoriasis, and erythema pernio, and came to like conclusions. Hallam<sup>20</sup> accepts their conclusions, saying: "The present state of our knowledge of calcium metabolism is admittedly deficient; but according to the investigations of Percival and Stewart already cited, there does not seem to be any justifiable ground for believing that either of these complaints (erythema pernio and acrocyanosis) is associated with, or consequent on, a calcium deficiency."

As we have stated, a normal calcium level in the blood may give no indication of the behavior of calcium in the body. In our opinion these patients were not given adequate calcium therapy, and we think that definite conclusions as to its efficacy are not warranted.

That irreversible changes in the arterial walls had not developed in any of our cases is shown by the normal appearance of the fingers and toes together with absence of symptoms whenever the surrounding

temperature was above the range in which attacks could occur. During high calcium treatment when the patient was exposed to cold, the symptoms either did not appear or were very much diminished; at higher temperatures the fingers and toes appeared normal, just as they did before calcium treatment. The effect of calcium in these cases is therefore presumably upon the peculiar hypersensitiveness of the blood vessels to cold, and not upon the normal vasomotor nervous control of the vessels.

In this respect the effect of calcium is fundamentally different from that of sympathectomy, which benefits spasmodic arterial disease only indirectly, i. e., by paralyzing the (normal) vasoconstrictor mechanism and so causing permanent vasodilatation. The extremities after sympathectomy are usually distinctly warmer than normal at all atmospheric temperatures, and are consequently less susceptible to the effects of cold. No apparent ill-effect is noted as a result of the loss of the pilomotor and sweating reflexes. Nevertheless, as Lewis emphasizes, the underlying hypersensitiveness to cold of Raynaud's disease persists, and can still be evoked by sufficiently prolonged exposure to cold.<sup>21</sup>

#### SUMMARY

Four cases are described in which there was spasmodic vascular disease of the Raynaud type characterized by hypersensitiveness to cold. Distinct benefit was obtained by a high-calcium-high-vitamin regime. The effect of calcium differs from that of sympathectomy in that no permanent alteration of the vasomotor nervous mechanism is brought about.

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## VENTRICULAR BIGEMINY (PARASYSTOLE OR RECIPROCAL RHYTHM) IN ATRIOVENTRICULAR RHYTHM\*

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CASES of atrioventricular rhythm with a certain type of ventricular bigeminy have been reported from time to time for many years. The electrocardiograms are characterized by conspicuous variation in the P-R and R-P intervals and by premature beats occurring at short intervals after the rhythmic ventricular contractions. The premature beat is not followed by a compensatory pause and it is preceded, in most of the reported cases, by a more or less well-defined P-wave. Authors who have reported such cases have employed two different theories to account for the second of the bigeminal beats. Both theories agree that the causative impulse is supraventricular in origin, but they differ regarding its exact site of origin and its character.

The advocates of the theory of *reciprocal rhythm* regard all auricular activity in these cases as due to impulses which originate in the A-V node. The cases differ from other instances of atrioventricular rhythm, however, in that the conduction of impulses from the A-V node *backward* to the auricle is interfered with. Contraction of the auricle consequently occurs at an interval after ventricular systole which grows progressively longer; i.e., the R-P interval increases. Conduction of the nodal impulses downward to the ventricle, on the other hand, is unimpeded, and this chamber responds without delay. But ventricular activity is not limited to the rhythmic impulses coming directly from the node. When the lengthening R-P interval reaches a certain value, a premature ventricular contraction occurs in response to an impulse from the auricle. By some it is supposed that the contraction of the auricle, set off by the nodal impulse, itself constitutes the stimulus to the premature ventricular systole. By others it is suggested that the nodal impulse in some way returns from the auricle, passing again through the A-V tissue and thus reaching the ventricle by a sort of circulating mechanism. In support of this notion its proponents cite Mines' classical experiment with the heart of a tortoise; an experiment, it will be recalled, which was concerned not with atrioventricular rhythm but with movement around a ring composed of both auricular and ventricular tissue.

Those who invoke the theory of *parasystole* believe that the auricular activity is due to impulses which originate, not in the A-V node, but at an independent pacemaker in the auricle. The rate of the auricular pacemaker is slower than that of the nodal pacemaker, and the progressive lengthening of the R-P interval results from this difference in rates. Under this theory, as well as under the other, *interference to the conduction of impulses from the A-V node to the auricle is assumed*. The interference, however, must be complete, thus guarding the center of slower rate from the faster center. But the block must apply to the passage of impulses only toward the auricle and not toward the ventricle. It must be unidirectional. For if impulses from the slower center were prevented from reaching the ventricle they could not excite it, and the resulting mechanism would constitute not parasystole but A-V dissociation. But since the block is only in the one direction, impulses elaborated at the auricular center as well as those from the A-V node pass toward

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the ventricle and themselves produce responses when not prevented by refractory tissue. Such ventricular responses to impulses from the auricular center, occurring before the sequential rhythmic impulse from the lower center is due at the ventricle, produce interruptions to the dominant ventricular rhythm.

Under both theories these cases are regarded as examples of so-called A-V rhythm in which the regular beating of the ventricle is interrupted by another supra-ventricular impulse whenever it finds the lower tissues responsive. One theory holds that both the auricle and the ventricle are activated from a single center located between them; asynchronism in contraction depending on unidirectional impairment in conduction. Under the other theory the auricle is activated from a center separate from that which activates the ventricle; asynchronism resulting from difference in the rates of the auricular and ventricular centers.

Before pursuing further the particular problem involved in the special cases of A-V rhythm with which this paper is concerned, brief consideration must be given to A-V rhythm itself. This name is given to a phenomenon produced under certain experimental conditions, particularly by destruction of the S-A node or by stimulation of the right vagus and the left sympathetic nerves. Under such circumstances the electrocardiographic complex of ventricular activity is not preceded by the usual form of P-wave at the usual interval. The P-wave is usually, but by no means invariably, inverted (Scherf and Shookhoff). Clinical electrocardiograms of similar form are similarly designated.

It is usually assumed, in explanation of such records both experimental and clinical, that a single focus somewhere in the A-V node has become the pacemaker and that impulses from it pass both to the auricle and to the ventricle. It is commonly held that different areas of the node may become such new centers of impulse formation, but orthodox opinion usually limits this to a single focus at a given moment and confines that center to the A-V node.

Geraudel has presented certain conceptions of impulse formation and transmission within the auricle, however, to which consideration must be given in any attempt to explain the mechanism of so-called A-V rhythm. He holds that there are several auricular centers which, developmentally considered, are natural areas of impulse formation; such areas not being embraced within the anatomical confines of the A-V node. Such a conception offers ready explanation of certain phenomena associated with A-V rhythm which are difficult to explain on the assumption that the node itself is the precise area of impulse formation. It explains also the different and varying shapes of the P-waves exhibited in experimental and clinical cases of A-V rhythm.

While it is agreed that suppression of the normal pacemaker produces "escape" from that area whose rhythmicity (or automaticity) is next in degree to that of the sinus, there is much evidence that this new pacemaker need not necessarily be within the A-V node, but that it may be at any one of several areas. Further suppression may dislocate the pacemaker to still another area. In the case of supra-ventricular extrasystoles it is indeed difficult in many instances to know whether the abnormal P-waves recorded in the electrocardiogram represent "nodal" or "auricular" extrasystoles and the difference between the two is growing less distinct.

The conception of A-V nodal rhythm which appears best to accord with experimental data is as follows: Under circumstances which depress impulse formation at the normal (sinus) area, another supra-ventricular area of impulse formation escapes. Further depression may suppress the second area and uncover another. That supra-ventricular area, in any case, whose automaticity at the moment is highest, becomes

the pacemaker. Rhythmic impulses originating in this pacemaker pass both toward the auricle and toward the ventricle. If conduction is unimpaired, both chambers respond to each rhythmic impulse. Other supraventricular areas of impulse formation then begin to build up impulses but are discharged before the completion of their rhythmic periods; the whole auricle as well as the ventricle responding to impulses from the dominant area. The location of this dominant area need not necessarily be within the A-V node in every case, the conception that it is so located having been based more upon assumption than upon experimental evidence. In many instances the new pacemaker appears to be "auricular" rather than "nodal." We employ the term atrioventricular rhythm with this conception, one somewhat broader, perhaps, than that usually implied by the term.

We have applied the theories of parasystole and of reciprocal rhythm to ten cases of atrioventricular rhythm of the particular type under discussion. The data in these cases collectively and in detail appear to elucidate the problem of mechanism. Study of them as a group reveals much evidence of intimate relationship between A-V rhythm, parasystole, and so-called reciprocal rhythm. The three rhythms appear to depend upon the same fundamental factors, the exact mechanism in different instances being determined by incidental differences in retrograde conduction from the dominant area. Just as a certain modification of retrograde conduction changes simple A-V rhythm into parasystole, so a different modification of retrograde conduction may produce that mechanism which has been called reciprocal rhythm. This conception will be elaborated after presentation of certain records by which it is strongly indicated. The cases not reported in this paper support the conception outlined above and might well be presented except for lack of space.

#### REPORT OF CASES AND DESCRIPTION OF ELECTROCARDIOGRAMS

CASE 1.—A white man of twenty-nine years was admitted to the Barnes Hospital, October 17, 1926, complaining of defective vision and headaches. There had been head trauma two months before admission. The past history was negative with regard to his heart. At examination it was noted that the area of cardiac dullness was slightly enlarged and that there was a systolic murmur at the apex, heard also over the precordium. The heart beats occurred in pairs. On October 25, 1926, a large endothelioma was removed from the left temporal region. During the operation his heart beat regularly. The patient made an uneventful recovery.

Electrocardiograms were made on October 18, 19, 21, during operation on October 25, and on November 6, 1926. Upon two of these occasions records were made following the intravenous administration of atropine sulphate in doses of 1/50 of a grain and 1/25 of a grain respectively.

The records are of four types. Specimens of each are shown in Figs. 1 and 2. In Fig. 1 we have indicated our conception of the mechanism by the drawings below the electrocardiograms. The record shown in the upper left-hand part of Fig. 1 was made during operation. The mechanism is normal and the area of





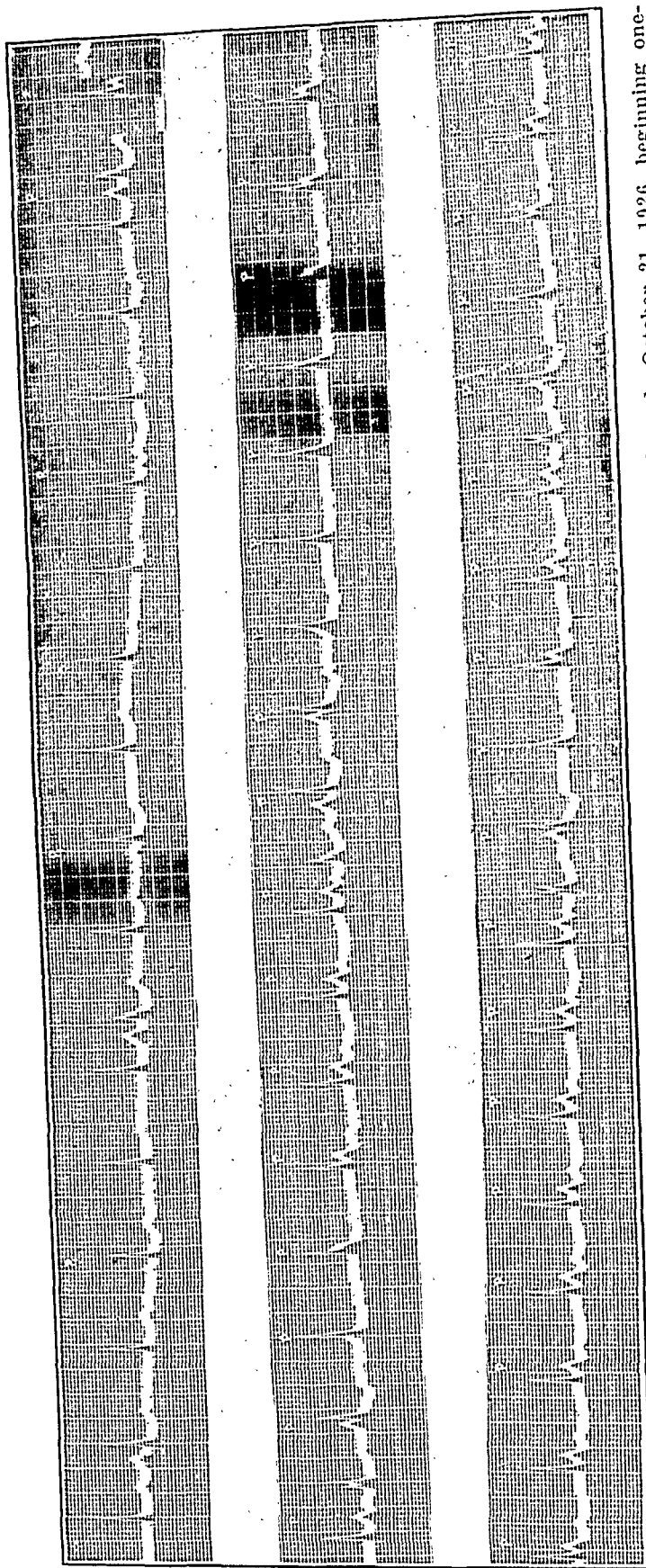


Fig. 2.—Electrocardiograms of the patient in Case 1. This is a continuous record in Lead II, made October 21, 1926, beginning one-half minute after the administration of  $1/25$  grain of atropine. Note the different shapes of the P-waves in the first part, and the rhythmic (large) P-waves in the last part. Note also the aberrant ventricular complexes following those P-waves which are properly spaced after R-waves.

impulse formation presumably is the sinus region. The electrocardiogram in the upper right-hand part of Fig. 1 is a record of the same type as the admission record. It shows ventricular complexes occurring in pairs, the first unaccompanied by an auricular wave but the second preceded by one at a constant interval. This P-wave is upright but its shape is different from that in the electrocardiogram made during operation in which the sinus P-wave appears to be depicted.

*Effect of Atropine.*—The last strip of Fig. 1 was recorded two and one-half minutes after 1/50 of a grain of atropine. Several P-waves with shapes different from that in the control and with short P-R intervals appear. Fig. 2 is a continuous record beginning 30 seconds after the administration of 1/25 grain of atropine. In the first part P-waves of two types are recorded. Those which predominate are similar to the ones recorded after the smaller dose of atropine. The others, which are larger, during the early effect of atropine occur only at rather long intervals, but under complete atropine effect they constitute the only type recorded. During the last 30 minutes of the atropine experiment they occurred regularly, and at a rate of 85 per minute. They are similar to the P-wave in the record made at operation and appear to represent activity originating at the normal pacemaker, while the smaller P-waves represent secondary pacemakers.

We interpret the second strip in Fig. 1 as follows: It records an independent ventricular rhythm with retrograde block between the ventricular\* pacemaker and the auricle. The degree of vagus stimulation responsible for this mechanism was sufficient to suppress the normal pacemaker. The auricle, therefore, receiving stimuli neither from the ventricular pacemaker nor from the sinus area, escaped at a secondary center. Impulses from this secondary area were conducted to the ventricle, exciting it to contraction. This constitutes true parasystole, the ventricle being activated by impulses both from the ventricular and from the secondary pacemakers.

The effect of small amounts of atropine was enough to uncover other secondary centers of impulse formation, but the full effect was required to uncover the sinus pacemaker. Atropine not only lessened vagus tone at the sinus area, but it accelerated the ventricular pacemaker as well, so that under its effect the rate of the ventricle still was faster than that of the auricle. Although at operation the sinus pacemaker dominated the rhythm, under 1/25 of a grain of atropine parasystole still obtained, the ventricular responses to impulses from the auricular center showing aberrant complexes. It will be noted that the pause following the aberrant ventricular complex is somewhat shortened. The explanation of this short interval has been given by Scherf and Shookhoff. They explain it as due to impairment of conductivity in the lower tissues resulting from the premature passage of the auricular impulse. This impulse is transmitted before the tissues have had sufficient rest and because of the accompanying conduction defect the P-R interval

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\*In the following pages the center of impulse formation from which the ventricle is activated will be referred to as the "ventricular pacemaker," that which activates the auricle as the "auricular pacemaker." By such designations we do not imply that these natural areas of impulse formation are located in the chambers activated by them.

The term "retrograde" as applied to the conduction of impulses will be used to mean conduction in a direction other than toward the ventricle. Retrograde conduction, therefore, is necessary in order for an impulse from the ventricular center to reach any secondary (and slower) center of impulse formation.

associated with the premature beat is prolonged. The aberrant complex, therefore, is set further to the right than it would be if conduction were at a normal rate, the following interval thus being encroached upon.\*

This incomplete recovery accounts also for the slight difference in shape shown by the T-waves of the ventricular complexes which follow the aberrant beat.

The fact that the auricular waves occur rhythmically and that this rhythm is undisturbed even in connection with the premature beat argues in favor of an independent auricular pacemaker. Inspection of this record alone, however, could hardly lead to a conclusion in the matter. But study of the case as a whole presents evidence which appears to admit of no other interpretation. The pairing of the ventricular beats recorded in the admission record (upper right of Fig. 1) could hardly be explained on the basis of so-called reciprocal rhythm. Such an assumption would meet difficulty in the long R-P intervals. The conclusion that the auricle is activated from a center or from several centers which are independent of the ventricular pacemaker is supported also by the variations in the shape of the P-waves which appear not only in different records but also in different parts of the same record. These variations would be hard to explain on the basis of difference in retrograde conductivity from a single pacemaker common to both ventricle and auricle.

*Summary of Case I.*—A case in which sinus depression resulted in escape at a secondary center. Impulses from this secondary center activated the ventricle but were not conducted to the auricle. The location of the pacemaker for the auricle varied, changing with vagus (and sympathetic) tone under such circumstances as a cerebral operation and the administration of atropine. Impulses from these various auricular centers, conducted to the ventricle, produced ventricular contractions when favorably timed, the response of the ventricle to such auricular areas as well as to the rhythmic ventricular center constituting parasystole.

*CASE 2.*—A colored man, aged sixty years, came to the Washington University Dispensary, February 2, 1928, complaining of increasing dyspnea, edema of the ankles and paroxysms of nocturnal dyspnea. Examination revealed emphysema, tortuous and sclerosed radial arteries, faint heart sounds and gallop rhythm. The rate was 80 per minute. There was no arrhythmia. The outline of cardiac dullness was ill-defined but it appeared to be somewhat increased to the left. The Wassermann reaction was negative. The blood pressure was 160/70. He had been taking digitalis, but the exact amount was not recorded. The tincture was then ordered, 15 drops three times a day. There was at first some general clinical improvement but this was followed by an increase in the number of attacks of nocturnal dyspnea. He returned to the dispensary at intervals until June 14, 1928, there being no notable clinical change during this period.

\*In some cases conduction has not fully recovered by the time of the next R-R interval and this also is slightly abbreviated.

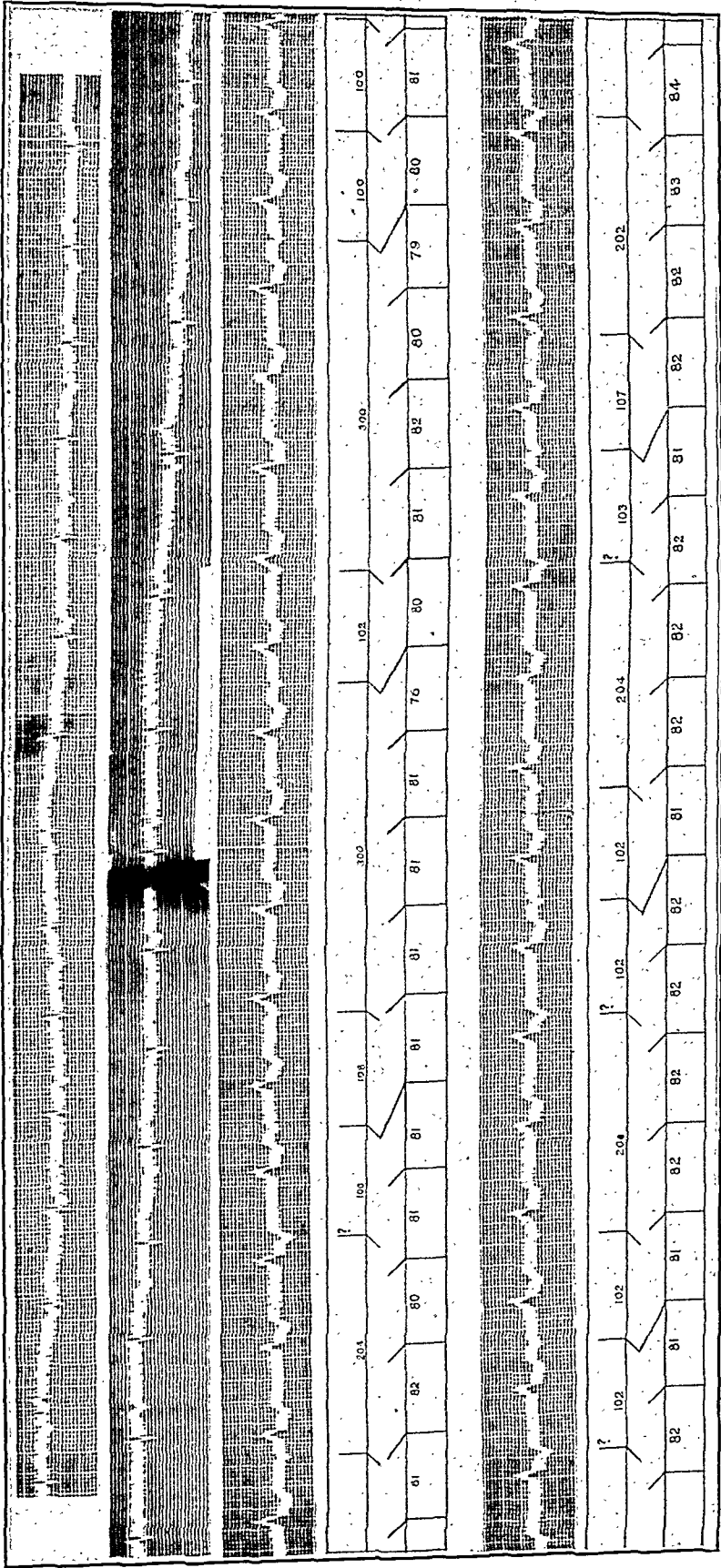


Fig. 3.—Electrocardiograms of the patient in Case 2, made June 9, 1928. The first and second strips are records in Lead III showing the effects of pressure over the right and left carotids, respectively. In the second strip the time of pressure is indicated by the signal at the bottom. In the first strip the pressure was applied just before the beginning of the fifth R-wave. The third and fourth strips are a continuous record in Lead II. Discussion in the text.

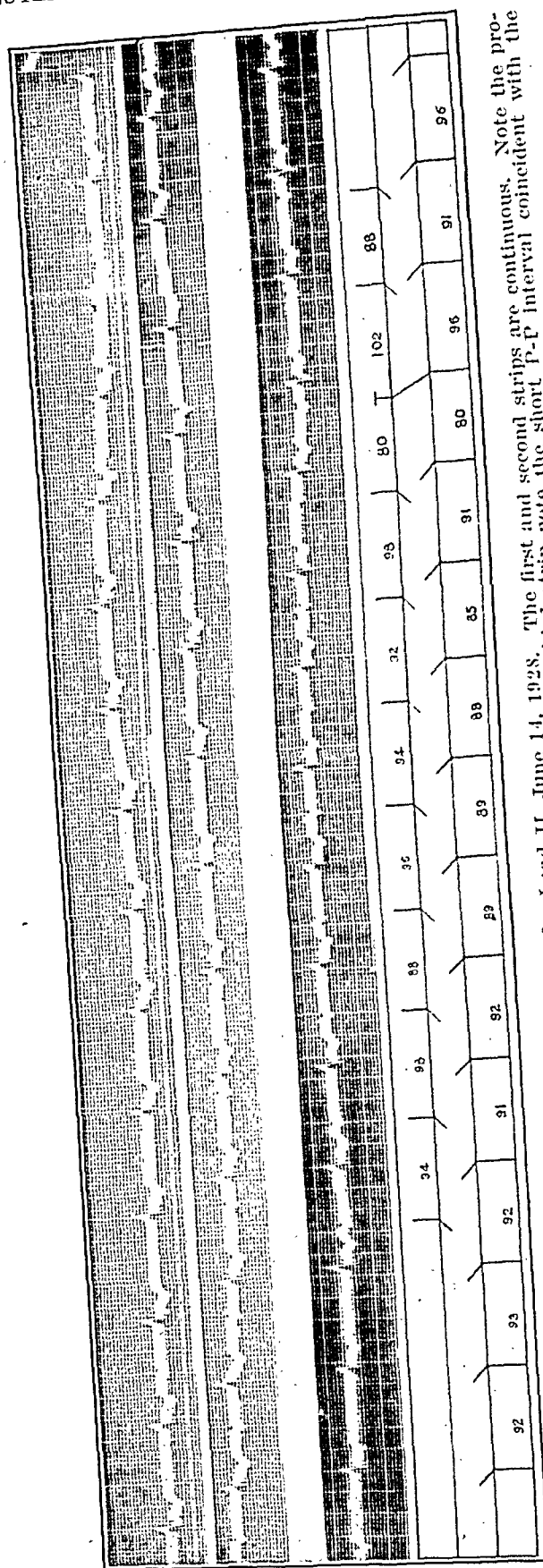


Fig. 4.—Electrocardiograms of the patient in Case 2, Lead II, June 14, 1928. The first and second strips are continuous. Note the progressive change in the position of the P-wave without notable arrhythmia. In the third strip note the short P-P interval coincident with the short R-R interval in the last third of the record. Discussion in the text.

Electrocardiograms were made upon five occasions. In the first two (February 2 and April 26) no arrhythmia is recorded, the P-waves are of normal shape and each is followed by a ventricular complex at a normal interval (0.17 of a second). In later records, parts of which are reproduced, the P-waves are of different shape and the normal P-R relationship does not obtain. The top strip of Fig. 3 is a record (June 9) in Lead III with pressure over the right carotid. It appears to show complete or almost complete dissociation between auricle and ventricle, the rate of neither having been affected by carotid pressure. Pressure over the left carotid, recorded in the second strip, caused a slowing of the ventricle but had little effect on the rate of the auricle. It will be observed that the rate of the ventricle (before carotid pressure) is 70-73, while that of the auricle is only 58-60. It will be noted further that the P-waves are inverted not only in Lead III but also in Lead II (third and fourth strips).

The first and second strips of Fig. 4 constitute a continuous record in Lead II made June 14. They are a part of a long record which shows a variation in ventricular rate from 62 to 71 and a variation in auricular rate from 58 to 65. At the beginning of the top strip the ventricular rate is 64 and no P-waves are clearly visible. P-waves soon appear, however, as notches on the right of the R-waves; and near the end of the top strip a definite T-P interval has developed, showing clearly defined P-waves with a rate of about 60. In the second strip this T-P interval increases progressively until the P-wave is lost in the succeeding R complex after which it emerges to the right of the *second* R-wave; all this without conspicuous arrhythmia either of the R- or of the P-waves. The ventricular rate in the second strip is about 62.

The A-V dissociation with the rate of the ventricle higher than that of the auricle, the regularity of the auricle with change in ventricular rate, and the abnormal shape of the auricular complexes appear to necessitate the following interpretation of the first and second strips of Fig. 3: Depression of the normal pacemaker with ventricular escape; retrograde block from the ventricular pacemaker, resulting in auricular escape at a secondary center; downward block from this secondary auricular pacemaker protecting the ventricular center from its impulses. This two-way block produces complete A-V dissociation.

It should be noted that this case presents two features in which it differs from the usual case of A-V block; the ventricular rate is relatively high and the P-waves are inverted. The first of these features is explained by the mechanism of origin. So-called A-V rhythm owes its inception to just such an abnormal relationship between the rate of the normal pacemaker and that of a secondary center. The second feature which differentiates this case from simple A-V block, i.e., the inverted P-waves, depends upon two factors. One of these also is inherent in its origin; the sinus area regularly is depressed in cases of this sort. The second is the distinguishing feature: the conduction of impulses backward from the ventricular center is blocked. Under such circumstances sinus depression leads to auricular escape at a secondary center.

Upon occasion one center may activate both chambers. It appears that the temporary improvement of conduction responsible for this phenomenon is always an improvement from auricle to ventricle, never

in the reverse direction. Removal of downward block at certain intervals is shown in the third and fourth strips of Fig. 3. These two strips are a continuous record in Lead II. In them a certain sequence is recorded again and again without variation; a P-wave stands about midway between two R-waves; in the next cycle it stands to the left of the R-wave; in the third cycle it is lost; in the fourth it modifies the T-wave, and in the fifth it appears again in the same position as at first. In a long record this sequence is unvarying and the conclusion is inescapable that the auricular and ventricular complexes in some way are related. The nature of this relationship is explained by further study of the record. It will be observed that the R-R interval associated with the long P-R interval frequently is short.\* Slight variations in rate are common both to the auricle and to the ventricle. If these short R-R intervals should be found to occur with synchronous changes in auricular rate, either might be thought to depend upon the other, or both might depend upon a common factor. But they are not so associated. Irrespective of the attendant auricular rate, the interventricular interval under consideration never is long: either it is short, or its length is not affected. This short interventricular interval is related, therefore, not to auricular rate, but to that particular auricular complex whose position in relation to it is constant. Every fifth auricular complex has this relationship and the conclusion follows that every fifth auricular impulse produces a ventricular contraction. These ventricular responses to auricular stimuli occur, however, only a little before the completion of the rhythmic ventricular periods, producing only slight shortening of the associated interventricular intervals. This results from the fact that the conduction defect is of considerable extent.

Instead of this relief of downward block occurring rhythmically as in Fig. 3, occasionally it occurs only in isolated instances. In the first strip of Fig. 3 the sixth interventricular interval appears to be an example. It is a little shorter than the others and in it a P-wave is situated in about the same relative position as the P-waves in the last strip that are associated with conducted auricular impulses. Another instance which gives better evidence of the occasional downward conduction of auricular impulses is shown in the bottom strip of Fig. 4. The fourth from the last interventricular interval is short. The associated interauricular interval also is short, and the shape of the P-wave which closes it differs slightly from that of the preceding P-waves. It is probable that this P-wave represents auricular response to an impulse originating at an area different from that which had been activating the auricle, and that this impulse also reached the ventricle.

Attention has been called to the fact that slight variations in rate

\*This is well shown in the tenth R-R interval of the third strip, resulting there in a definite, though not conspicuous, ventricular bigeminy.



occur at both the auricular and the ventricular pacemakers. In portions of some of the records in which the interpretation is equivocal it is probable that the uncertainty is due to a changed relationship between the rates of the two pacemakers rather than to a change in mechanism. Fig. 4 is a case in point.

The second part of this record (middle strip of Fig. 4) would appear to admit of only one interpretation, viz., independent auricular and ventricular pacemakers with rates almost identical, but with the rate of the ventricular center a little faster than the other. In the first strip, however, the alternative explanation of a single pacemaker for both auricle and ventricle must be considered. If the first part were studied alone, the temporary absence of visible P-waves and the nearly identical rates of auricle and ventricle might favor that interpretation. It is conceivable that temporary improvement in conduction might have allowed one pacemaker for a short time to activate both chambers. But study of the whole record (as well as other records in the case) suggests change in rate rather than change in conduction as the correct explanation of the difference between the two parts of the record, and indicates that the beginning as well as the following parts of the record in Fig. 4 represents separate auricular and ventricular pacemakers. The rates of the two pacemakers are not far apart to begin with and only a slight change of either would be required to make them nearly identical. In Fig. 4 the difference between the rates of the auricle and the ventricle is not as conspicuous as it is in Fig. 3. It is on this account that the interpretation of mechanism is less readily apparent in Fig. 4.

*Summary of Case 2.*—A case of sinus depression with ventricular rhythm, impulses from the ventricular center failing to reach the auricle. The depression of the normal pacemaker is of such extent that auricular escape occurs at a secondary area. Not only is retrograde conduction from the ventricular center depressed but there is also such impairment of downward conduction from the secondary auricular area that its impulses rarely reach the ventricular center. The result is almost complete dissociation between the secondary auricular and the ventricular centers, the ventricle being activated only rarely by impulses from the auricular center.

*CASE 3.*—A colored woman, forty-two years of age, was admitted to the Barnes Hospital, December 15, 1926, complaining of dyspnea and cough. Nine years previously she had had some sort of acute arthritis. The dyspnea was of several years' duration and for a few months she had been incapacitated. She had been taking 60 drops of tincture of digitalis daily for ten weeks before admission. Examination revealed generalized edema, an enlarged liver, and diminished breath sounds over the right base of the chest. The heart was conspicuously enlarged to the left and both a systolic and a diastolic murmur were heard over the precordium. Extrasystoles were noted. The systolic blood pressure was 125, the diastolic, 55 mm. The Wassermann reaction was positive. Following a short period of improvement

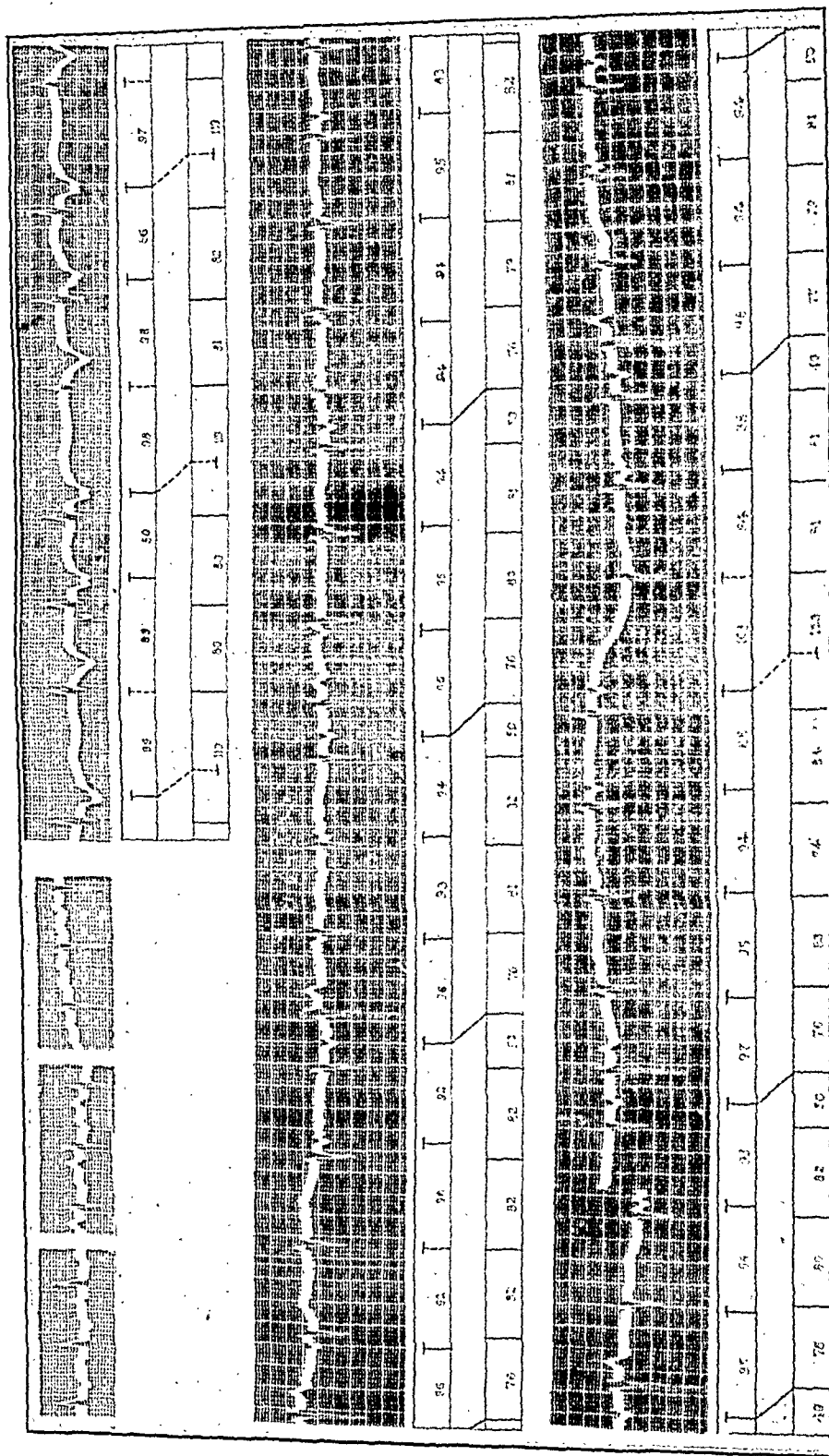


Fig. 5.—Electrocardiograms of the patient in Case 3. At the left of the top strip are shown the three leads of the admission record; at the right is the record in Lead I made December 29, 1926. The middle and last strips are a continuous record in Lead III made December 30, 1926. Discussion in the text.

she became worse and after a variable course she died March 3, 1927. Postmortem examination revealed a thrombus adherent to the wall of the right auricle, hypertrophy and dilatation of the heart and syphilitic disease of the aorta and of the aortic valves.

Electrocardiograms were made upon five occasions. The one made upon admission (Fig. 5, upper left part) shows no abnormal rhythm, but later records show the independent ventricular rhythm, inverted P-waves and premature ventricular complexes characteristically situated (see middle strip of Fig. 5), features which put them in the category under discussion.

From the evidence presented in Cases 1 and 2 and which will be elaborated below, this case appears to be an instance of parasystole involving ventricular and secondary auricular pacemakers. It is presented because of two additional features not shown in the other cases. One appears to have no bearing upon the general problem of mechanism but offers important evidence upon a related question. It consists in a certain modification of ventricular rhythm as follows: In some of the places where the premature beat regularly occurs none is recorded, but the location of the following ventricular complex is exactly what it would have been had the premature beat occurred. (See bottom strip of Fig. 5.) Comment upon this modification of ventricular rhythm will be reserved for a subsequent footnote.

The other special feature of this case, however, furnishes evidence of great importance to the problem with which this paper deals. It relates to the auricular rhythm. The basic rhythm of the auricle in this, as in other cases, shows slight variations. The interauricular intervals vary between 0.92 of a second and 0.96 of a second (middle strip of Fig. 5). Upon occasion, however, that interval which precedes the break in ventricular rhythm is shortened, an interval of 0.88 of a second being recorded in three instances. Upon other occasions slight shortening of this interval is suggested, but in view of the arrhythmia throughout the record, no such special feature in these other instances can be demonstrated.

The P-waves which close these short intervals and whose early occurrence is responsible for the abbreviation, have a characteristic position. They occur at about 0.20-0.22 of a second after the beginning of the preceding R-wave. P-waves which occur earlier with reference to R-waves never are premature. In other words, whenever the rhythmic occurrence of an auricular complex would place it nearer to the R-wave than 0.20 of a second, it falls at its rhythmic interval. But if the completion of its rhythmic interval would cause it to fall at a time after R greater than 0.22 of a second, it occurs prematurely. In occurring prematurely, moreover, it is never closer to R than 0.20 of a second. This invariable relationship to the preceding ventricular beat can hardly be fortuitous. The simplest explanation, and indeed the only one that appears to us at all probable, is that the impulse from the ventricular center discharges the auricular pacemaker if it arrives at the time when

the auricular stimulus is about to be spontaneously discharged. That it does not thus affect the auricular center in the cases of those P-waves which are inscribed earlier with reference to R and 0.20 of a second indicates that the conduction of the impulse backward from the ventricular pacemaker is impaired.\*

When the auricular pacemaker is discharged prematurely one would expect the length of the following P-P interval to be unaffected. In certain instances such is the case (e.g., at the beginning of the bottom strip of Fig. 5. See also upper right-hand strip at top of Fig. 5). Upon other occasions, however, it is somewhat prolonged and this lengthened period requires explanation. In such instances it is possible that the early occurrence of the auricular beat is due to the elaboration of a stimulus at a secondary center of impulse formation, a phenomenon recorded in some of our other cases. What appears to be probable, however, is that such a secondary center located near the dominant auricular pacemaker has been discharged by the impulse from the ventricular pacemaker. This explanation is supported by the fact that even in such instances the position of premature P-waves with reference to the preceding R-wave is the same as upon other occasions.

The impulse which is prematurely discharged produces an auricular contraction and passes toward the ventricle just as do other impulses from the auricular pacemaker. Unless its passage is interfered with it elicits a ventricular contraction. As in the case of the rhythmic impulses, whether or not it does so depends upon the time relationship of its occurrence to events below it. If it finds the lower tissues responsive a premature ventricular beat occurs.

The premature auricular impulse which is shown above the broken diagonal line near the middle of the diagram accompanying the lowest strip in Fig. 5 does not elicit a ventricular response. But although the ventricle fails to beat in response to this auricular impulse, the next beat of the ventricle takes place not after the rhythmic interventricular interval but at that time when it would have occurred had a ventricular contraction followed the auricular impulse. *The ventricular pacemaker appears to have been discharged without effecting a contraction of the ventricle.*† The same phenomenon is recorded regularly in the right-hand part of the top strip of Fig. 5.

Our explanation of the occasional short P-P interval as due to incomplete retrograde block from the ventricular center cannot be proved.

\*This paper is not primarily concerned with theories of block. Whether impulses from the ventricular pacemaker fail to excite the auricular center on these other occasions because they do not reach it, or because upon arrival they find it less responsive, we do not attempt to say.

†Much has been written regarding the site of delay and of block in cases which exhibit a prolonged P-R time or a failure of ventricular response to an auricular impulse. The evidence in our records just referred to supports the contention of Scherf and Shookhoff that the block is in the tissues of the A-V bundle below the A-V node. Or rather in our case it is below the ventricular center of impulse formation. This deduction follows from inspection of the record. Attention has been directed to the fact that the interventricular interval following the premature ventricular beat is not prolonged. This results from the discharge of the ventricular pacemaker by the passage through it of the auricular impulse. After its discharge the ventricular center elaborates another impulse at its regular interval. Upon this all authors are in agreement. The records in Fig. 5 indicate, however, that although the ventricular center was discharged by the auricular impulse, *no ventricular response was elicited*. The sequence of events in this part of the curve is exactly the same as it is in analogous parts except that the QRS complex is missing. If the auricular impulse discharged the ventricular center, therefore, and yet did not excite the ventricle, the failure of ventricular response was due to incomplete re-bearing upon the question at issue in this paper, it is, so far as we are aware, a unique record and because of its apparent bearing upon the problem of block it is reproduced.

Those who have interpreted such records on the basis of reciprocal rhythm explain not only the premature auricular impulse, but all others as well, as originating in the ventricular center. This record alone cannot disprove such a theory. Both the theory of a single pacemaker and that of dual pacemakers assume a conduction defect from the ventricular pacemaker to the auricle. As applied to this record, however, the conception of a single pacemaker necessitates the assumption of a sort of haphazard change in conductivity in order to explain the auricular arrhythmia. The theory of dual pacemakers explains the auricular arrhythmia as due to the mathematical relationship between the time of arrival of the (retarded) impulse and the rhythmic period of the auricular pacemaker. The agreement of this explanation with recognized physiological principles and the general similarity of the records in this case to those in other cases in which two pacemakers appear to be demonstrated will be presented as evidence favoring the conception that these cases of so-called reciprocal rhythm are but modified forms of parasystole.

*Summary of Case 3.*—A case of sinus depression with ventricular rhythm and impairment of retrograde conduction from the ventricular center. The guarding of the auricular pacemaker from the ventricular center was not quite complete, and occasionally the elaboration of an auricular impulse was hastened by the arrival of a stimulus from the ventricular pacemaker. The ventricle responded to auricular impulses unless prevented by refractory tissue, such responses together with those from the ventricular center constituting parasystole.

#### GENERAL DISCUSSION

The modification of simple atrioventricular rhythm which produces the mechanism shown in the cases of this group can be fully appreciated only in its relationship to the fundamental mechanism of uncomplicated cases. Atrioventricular rhythm originates under conditions which depress the sinus area or which exalt another center of impulse formation; or under conditions which produce both effects. The result is that secondary centers of stimulus production are uncovered. That center whose automaticity is highest will dominate all others, in the manner described above, provided impulses from it are freely conducted to them. Impulses from the dominant area, under such circumstances, activate both the auricle and the ventricle. Such a case, with no impairment of conductivity, falls into the category of simple atrioventricular rhythm.

If there is a defect in retrograde conduction, however, a modification of this simple mechanism results. Impulses from the dominant area, in some cases, while freely conducted to the ventricle, are not conducted to the auricle. There is retrograde block. Under such circumstances the auricular center of impulse formation whose degree of automaticity

is next in order escapes,\* and impulses *from it* activate the auricle. Just which of the natural centers of impulse formation will become the pacemaker for the auricle in a given case depends upon circumstances.\*\* In one case it may be the sinus area (Case 1); in other instances sinus depression may lead to escape at a lower center (Cases 2 and 3). The shape of the P-waves, therefore, will differ in electrocardiograms of different cases. In an individual case, moreover, changes in vagus tone may depress that area which has been dominant and uncover another. The shape of the P-waves, therefore, may vary in the same record (Case 1). The rate of such a secondary auricular center is necessarily slower than that of the ventricular center; for if it were not slower this auricular center itself would have assumed the rôle of pacemaker and its impulses would dominate the ventricular rhythm. The blocking between the two centers in most instances, moreover, is only in the one direction, impulses from the secondary center being conducted to the dominant center and discharging it prematurely when not prevented by refractory tissue. Such cases fall into the category of parasystole.

It will be observed that the difference between cases of A-V rhythm which exhibit parasystole and those which do not is a difference in the retrograde conduction of impulses from the ventricular pacemaker. In one class of cases impulses are readily conducted backward, in the other they are blocked. There may be intermediate stages of retrograde conductivity, however, corresponding to well-known differences in downward conductivity. In certain cases the impairment, while considerable, is not complete (Case 3). There is partial retrograde block. In such a case the dominant auricular center will discharge its impulses rhythmically when it is undisturbed by impulses from the faster center. Under certain circumstances, however, it may be discharged prematurely by the arrival of an impulse from the ventricular center. This occurs only when the ventricular impulse reaches the auricular center near the end of its automatic period.† The impulse from the auricular pacemaker, when prematurely discharged, spreads exactly as it does when automatically released, activating the auricle and, unless interfered with, the ventricle as well. In such cases the impairment of conductivity from the faster center to the slower, while sufficient to prevent the one from dominating the other completely and thus establishing simple A-V rhythm, is yet not great enough to allow the develop-

\*"Escape" from a natural center of impulse formation is a well recognized phenomenon. It can occur from a center whose rate is below that of the dominant area only when the slower center is protected from the faster. It explains the origin of the ventricular impulses in cases of ordinary A-V block. In such cases it is the ventricular center which is protected from a faster area. The protecting block, moreover, is in the reverse direction, i.e., downward block. In complete heart-block (A-V dissociation) there is, of course, upward block as well. Otherwise the auricular pacemaker would occasionally be discharged by impulses from below and auricular parasystole would result.

\*\*Muscular lesions as well as vagus tone may be important factors. †The same phenomenon has been observed in certain cases of partial A-V block, dissociation being almost but not quite complete. Although an independent ventricular rhythm may have been established, the ventricle occasionally may beat in advance of its rhythmic period in response to such auricular impulses as arrive just before the automatic ventricular impulse has matured.

ment of pure parasystole. The resulting mechanism stands between these. It is a modified form of parasystole. It depends upon the discharge of impulses not from a single pacemaker but from two pacemakers. When bigeminal beating of the ventricle occurs in such instances, the second beat is in response to an impulse whose immediate origin is different in place but similar in character to that which excites the first beat.

It is the occurrence of premature ventricular beats associated with interauricular intervals thus abbreviated, in cases of atrioventricular rhythm, that has fortified the arguments of those who explain not only these but other instances of bigeminy in A-V rhythm as due to "reciprocal rhythm." The dependence of the second beat upon the first is indicated by the constant relationship between them and the conclusion that the first beat is "in some way" responsible for the second is a sound one. The further conclusion that the auricle is concerned in the causation of the second beat also is sound. But neither the deduction that the *original impulse* which causes the first beat again returns to the ventricle, nor the assumption that it is the stimulus of auricular systole, *auricular contraction itself*, which produces the second beat appears to us to be warranted. Such conceptions imply either that the impulse causing the second beat is identical with that concerned with the first in point of origin or that it differs from it in character. Neither proposition appears to be supported by theoretical considerations, by experimental evidence or by clinical records.

That an impulse enters the auricle by a certain path, proceeds in some unknown way, returns to its point of entry and then proceeds again over the same path of entry but in opposite direction . . . all this should not be hypothecated simply because under certain experimental conditions instances of circulating mechanism involving a known path have been observed. The hypotheses requisite for an explanation of the premature beat on the basis of parasystole, on the other hand, accord with recognized physiological concepts. Different degrees of conductivity backward as well as forward; separate areas of stimulus production; escape from one of these areas; the anticipation of a rhythmic beat by a stimulus from another center; none of these postulates is at variance with established conceptions of cardiac mechanism. Cases of parasystole, furthermore, are on record, in which the interpretation is unequivocal. Few, if any, of the cases reported as "reciprocal rhythm" appear to necessitate such a separate interpretation.

A comparative study of the records in our cases strongly indicates that the mechanism in these instances in which short P-P intervals are associated with the premature ventricular beats is fundamentally the same as that which obtains in cases with no auricular arrhythmia. This conclusion is indicated both by the general similarity between the two kinds of records and by the fact that in a single record both phenomena

appear (Case 3). It would be difficult to harmonize the conception of a single pacemaker with regularity of auricular beats associated with ventricular bigeminy (Case 1; also certain records in Case 2).

Case 2 is peculiarly important. The records indicate that, not only was there complete block from the ventricular to the auricular pacemaker (retrograde block), but that there was impairment of conductivity in the other direction as well. Not only was the auricular pacemaker guarded from the ventricular center but in addition the ventricular pacemaker was guarded from the auricular center. In most of the records there appears to be complete dissociation between the two pacemakers. Under certain circumstances, however, it appears that the downward block was not quite complete and that occasional impulses from the auricular pacemaker excited the ventricle to contraction. We do not see how the records in this case could be interpreted on the basis of a single pacemaker. It appears to be a case of A-V block (almost but not quite complete) in which the sinus area has been suppressed and another center has become the auricular pacemaker. Or rather, from the viewpoint presented above, it is a case of A-V rhythm in which there is interference to the conduction of impulses from the ventricular pacemaker backward to the auricle, resulting in escape at a secondary center; and in which there is at the same time interference to the conduction of impulses from the auricular pacemaker downward to the ventricle. This impairment of downward conduction, if complete, would remove the case from the category of parasystole; for ventricular responses to impulses from the upper center would be impossible in that event, and parasystole could not develop. Such a case presenting evidence of *two sub-sinus pacemakers* discharging impulses simultaneously is of great importance to the question at issue.

This conception of so-called atrioventricular rhythm as a mechanism which may involve a single pacemaker, or which may involve two pacemakers, the one more or less completely guarded from the other, or (rarely) both guarded from each other, appears to us to be necessitated by comparative study of the cases reported. The fundamental relationship, therefore, between cases of simple A-V rhythm, of so-called reciprocal rhythm and of parasystole is at once apparent; the precise mechanism in a given instance being determined by the degree of retrograde conductivity from the ventricular pacemaker.

#### SUMMARY

In atrioventricular rhythm the normal auricular pacemaker is inhibited and there is uncovered a secondary center from which impulses activate the ventricle and, in uncompleted cases, the auricle as well. In certain cases, however, impulses from the secondary center are not conducted to the auricle. In such instances auricular escape occurs, the auricular center of highest automaticity becoming the pacemaker for



the auricle. The rhythmicity of such a secondary auricular center is subject to the same influence that may affect other centers of impulse formation. In some cases the retrograde blocking of impulses from the ventricular center is incomplete, and the auricular pacemaker is discharged prematurely by those impulses which reach it just before the completion of its automatic period. Impulses from this pacemaker pass not only to the auricle but also toward the ventricle and produce premature ventricular contractions when not interfered with by refractory tissue. Beating of the ventricle in response to impulses both from the ventricular pacemaker and from the auricular center in such cases constitutes parasystole.

Ten cases were studied, three of which are reported in detail. Reciprocal rhythm as an explanation of the records in these cases is considered but evidence against this interpretation is presented. It appears that cases of simple A-V rhythm, of so-called reciprocal rhythm, and of parasystole are fundamentally related; the precise mechanism in a given instance being determined by the state of retrograde conductivity from the ventricular pacemaker.

These cases occur under circumstances associated with sinus depression and lowered conductivity. Digitalis in some instances appears to be a contributory factor.

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# A STUDY OF GALLOP RHYTHM BY A COMBINATION OF PHONOCARDIOGRAPHIC AND ELECTROCARDIO- GRAPHIC METHODS\*

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THE application of phonocardiographic methods is destined to render useful service in the study of gallop rhythm. The first records published are not of much clinical interest. The tracings are lacking in precision, and the minute details so useful for the interpretation of the sounds are not in evidence. No doubt these faults are to be attributed to the imperfections in the apparatus employed.

A great advance was made with the introduction of precise photographic methods. By the simultaneous application of sound waves with other cardiac tracings, whether those of the radial or carotid pulse, or the electrocardiogram, a further advance was made.

The simultaneous electrocardiogram enables us to draw most valuable conclusions because of the precision of its waves and by its immediate transmission. The second tracing is indispensable for the correct interpretation of the phonocardiograms.

One has only to consult the researches of Lewis,<sup>14</sup> Groedel,<sup>8, 9</sup> Battaerd,<sup>2</sup> Bull,<sup>3</sup> R. H. Kahn,<sup>11</sup> Weiss and Joachim,<sup>21</sup> Selenin and Vogelsson,<sup>19</sup> H. Mond and Oppenheimer<sup>17</sup> and ourselves<sup>15, 16</sup> in order to appreciate the advantages of these simultaneous tracings over the single phonocardiograms.

In our study we have used a simple optic phonocardiograph with electric valves which we ourselves have constructed.<sup>5</sup>

Our apparatus registers the phonogram on the same film as a string galvanometer record. The results and the conclusions which we publish here on gallop rhythm are drawn from tracings made according to this method.

We must insist here upon the fact that gallop rhythm does not always have the same origin. We shall leave out of the discussion all varieties of gallop rhythm not of auricular origin and shall confine our attention to *classical auricular gallop rhythm*.

Typical gallop rhythm is produced by the addition to the two normal sounds of a sound auricular in origin or more exactly auriculoventricular. This sound is considered as the result of the shock of the auricular blood wave on a hypotonic ventricle. Almost all authors agree to this explanation of the rhythm which we are about to discuss. Gallop rhythm as such is not of sudden origin. At the beginning it is often indistinct, and the term gallop rhythm cannot be correctly applied at

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this moment. Afterwards this indistinct gallop may disappear altogether or may develop into a real triple rhythm. We shall see that these modifications of the heart sounds which precede the appearance of gallop rhythm are due to auricular phenomena.

For this reason we shall deal not only with well-developed cases of gallop rhythm but also with the indistinct forms referred to above. We shall extend our discussion to several cases of Stokes-Adams disease with their auricular sounds and to other still rarer affections where an auricular sound is perceptible.

Our group of tracings will thus deal with all added *sounds* (not murmurs) of auricular origin including those which do not necessarily constitute cases of gallop rhythm (23 cases of gallop rhythm in 33 observations).

The observations can be classified as follows:

- 20 cases of hypertension,
- 5 cases of hypotension,

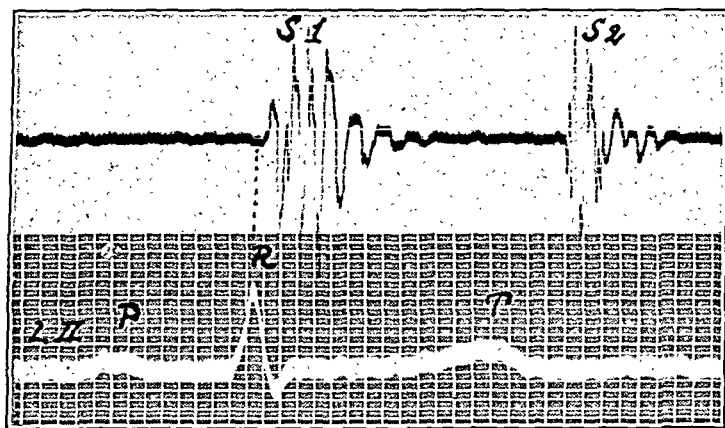


Fig. 1.—Phonogram and electrocardiogram taken simultaneously on a normal subject. The first sound ( $S_1$ ) begins at the crest of the wave R. The second sound ( $S_2$ ) appears 0.03 sec. after the end of the wave T. Timing = 1/50 sec.

- 3 cases of Stokes-Adams disease,
- 2 cases of extrasystolic arrhythmia,
- 2 cases of mitral disease,
- 1 case of congenital heart disease.

In all the cases the auricular origin of the added sound is shown by the presence of the P-wave of the electrocardiogram.

Before undertaking the study of pathological tracings a few remarks should be made upon the chronological relations of the phonogram and the electrocardiogram under normal conditions. A normal tracing is shown in Fig. 1.

The first heart sound begins at the crest of the R-wave of the electrocardiogram and never before it.\* It can, however, appear after the crest

\*Bridgman<sup>1</sup> and Groedel<sup>10</sup> describe a "normal presystolic sound" which we also have found in some cases, but it is auricular in origin.

of the R-wave in certain cases. It is important to bear in mind this indication in reading the tracings of gallop rhythm which follow. Accordingly no oscillation of the phonogram situated before the R-wave can belong to the first ventricular sound. We attribute the existence of such oscillations in all our observations to the effect of the auricular contraction.

# GALLOP RHYTHM IN HYPERTENSION

The observations which follow illustrate the three principal forms of gallop rhythm which one encounters. They correspond at the same time to three different degrees of gravity of the affection. We shall see further on that these forms are the most common. There are others, however, which do not fit exactly in this somewhat rough presentation.

CASE 1.—Male sixty-four years old, arterial tension, 210/140 mm. of Hg. Albuminuria; complaining for some weeks of dyspnea and tachycardia, with violent pains in the head. Blood urea, 68 mg. Auscultation of the heart reveals the first heart sound dull and prolonged in the midcardiac area. The second sound especially accentuated. No murmur at the different areas.

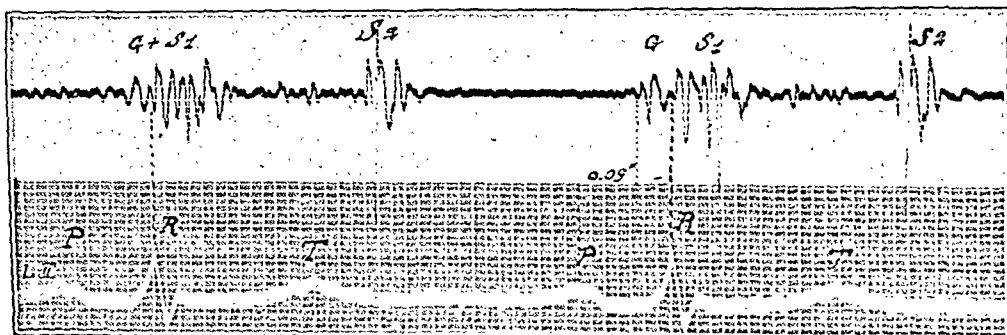


Fig. 2.—Hypertension and albuminuria, slight decompensation. Phonocardiogram and EKG. Male, sixty-four years old. First sound prolonged in the midcardiac area by a short auricular sound (G) jointed to the first sound (S<sub>1</sub>). Second sound (S<sub>2</sub>) accentuated. Space P-G = 0.09 sec. Immediate and subsequent prognosis good. G disappeared after a short period with remarkable clinical amelioration.

On considering the phonocardiogram (Fig. 2) we notice that the first sound is longer than a normal heart sound. It lasts 0.15 sec. instead of the normal 0.10 sec. The electrocardiogram taken simultaneously furnishes the explanation. It is obvious in fact that two important oscillations precede the R-wave. Their auricular origin cannot be questioned, when we consider the position and the presence of the preceding P-wave.

The case under discussion is not exceptional. It is commonly met in cases of hypertension at the beginning of decompensation. The modification in the auscultatory signs is due to the addition of a slight auricular sound intimately connected with the first ventricular sound. On account of this special chronology the addition of the sound does not give rise to gallop rhythm. It produces a presystolic prolongation of the first sound which should be considered as precursor of gallop rhythm.

CASE 2.—Deals also with a case of Bright's disease. Male, forty-nine years old. In this case, cardiac decompensation is more advanced than in the preceding one.

Effort tachycardia, dyspnea, edema of the feet at the end of the day, albuminuria. Blood urea 68 mg. Arterial tension 205/150 mm. Auscultation at the same time as the taking of the tracing reveals the presence of gallop rhythm produced by the addition to the two heart sounds of a third sound, dull, presystolic, badly defined. For this reason the two first sounds of the rhythm are not clear.

Fig. 3 (Case 2) shows an important group of oscillations of the phonogram before the R-wave of the EKG. This is explained by the auricular contraction P. The lack of distinctness in the rhythm is due to the

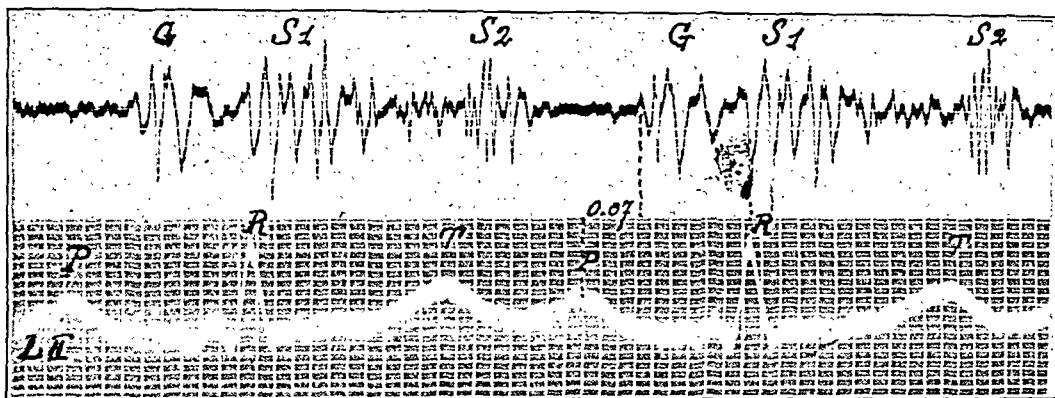


Fig. 3.—Hypertension and albuminuria. Notable decompensation. Male, forty-nine years old. Phonocardiogram and EKG. Indistinct gallop rhythm. Auricular presystolic sound (G) not distinctly separated from the first sound ( $S_1$ ). The second sound ( $S_2$ ) is weak. Space P-G = 0.07 sec. Fair clinical prognosis, conditions stationary during the previous six months. Gallop rhythm established during the last two years.

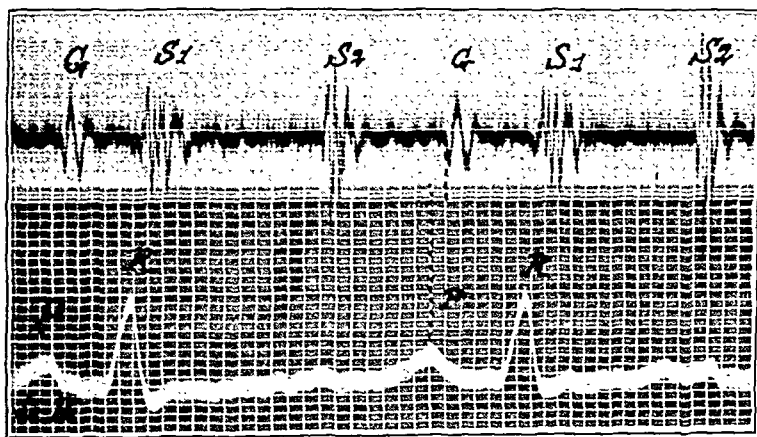


Fig. 4.—Chronic nephritis, terminal cardiac decompensation. Female, forty-seven years old. Phonocardiogram and EKG. Gallop rhythm distinct on auscultation and palpation. Auricular sound (G) presystolic, well separated from the first heart sound ( $S_1$ ) (silence of 0.08 sec.). Second sound ( $S_2$ ) accentuated. Space P-G = 0.03 sec. Clinical conditions very bad. The patient died three weeks after the taking of the tracing.

shortness of the silence which separates the two first periods. This lack of distinctness is further accentuated by their dullness.

CASE 3.—Bright's disease. Female, forty-seven years old, in a very advanced stage of decompensation. Obligated to remain in bed during the past months, with pronounced swelling of the legs. Permanent dyspnea and albuminuria. Blood urea 30 mg. Auscultation reveals a distinct gallop rhythm accompanied by a presystolic shock which could be easily palpated. Arterial tension 210/150 mm.

The tracing (Fig. 4) reveals the existence of a presystolic sound separated from the first sound by a complete silence of 0.06 sec. This is the classical gallop rhythm which can be perceived equally well by palpation and by auscultation, and the significance of which for the prognosis is well known. The patient died shortly after the taking of the tracing. Post-mortem findings by Professor Askanazy revealed sclerosis and atrophy of the kidneys, considerable hypertrophy of the myocardium—ventricular and auricular—with dilatation of the heart chambers, as is usual in these cases.

In decompensated hypertension the distinctness of the gallop rhythm does not always correspond in such a striking fashion with the gravity of the disease, as in the three cases cited. A certain proportion of such patients may possess a well-defined gallop rhythm for years before declining. Fig. 5 deals with an example of such cases: Female, seventy-

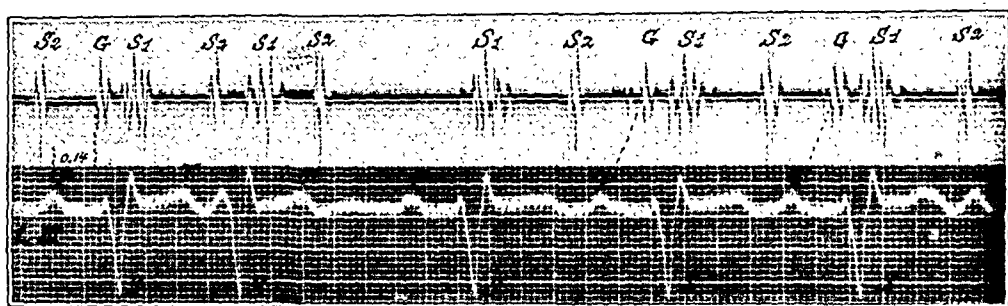


Fig. 5.—Female, seventy-six years old. Hypertension, albuminuria, slight effort dyspnea. Arterial tension 180/130. Phonocardiogram and EKG. Well defined gallop in evidence by auscultation and palpation for the past two years. Auricular sound (G) short and loud, separated from the first heart sound by a silence of 0.14 sec. Extrasystole of septum origin followed by a compensatory pause after which gallop rhythm is absent. The space P-R of the EKG is increased (0.24), a fact which contributes to the distinctness of G (in spite of the length of the space P-G = 0.14 sec.). Second sound is intense (S<sub>2</sub>). Clinical status gives no immediate cause for alarm.

six years of age, with gallop rhythm during a period of two years, in whom the clinical conditions became no worse.

(We shall discuss later the different factors which influence the distinctness of gallop rhythm.)

#### GALLOP RHYTHM IN ARTERIAL HYPOTENSION

Gallop rhythm in hypotension, the clinical picture of which has been so well defined by Dumas,<sup>6</sup> owes its origin in almost every case to the classical mechanism of the auriculoventricular shock. In its category, however, the third heart sound is more frequent than in hypertension and can give rise to triple rhythms which must not be confused with presystolic gallop.

Gallop rhythm of hypotension occurs in primary affections of the myocardium, in hemorrhagic shock, in certain diseases such as leucemia and pernicious anemia, and finally in infectious diseases which affect the heart, such as typhoid fever.

We have never had an opportunity to observe indistinct forms of this

gallop comparable with Case 1, previously cited. We do not doubt, however, the existence of such. In the five cases which we have followed, the rhythm is always well defined and in general more distinct than that of hypertension gallop. The tracings of Fig. 6 relate to a patient forty-

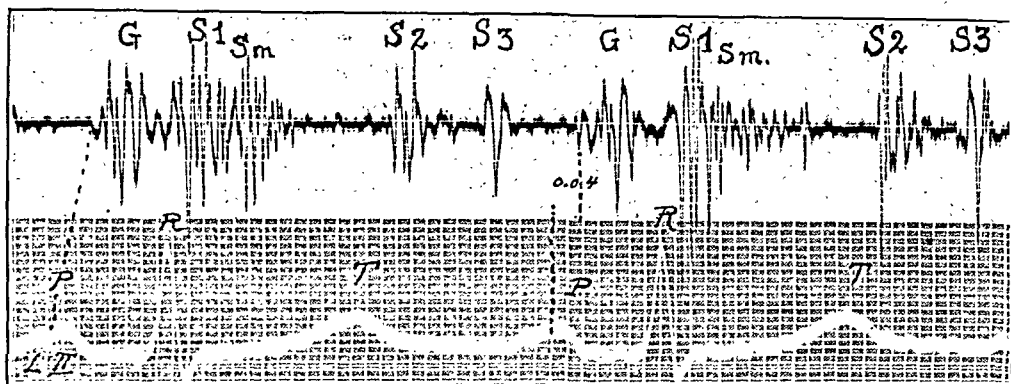


Fig. 6.—Pernicious anemia. Male, forty-nine years old. Hb. 40 per cent, red blood cells 1,225,000. Arterial tension 90/60 mm. Four-time rhythm at the apex. Presystolic sound (G) intense and of high tone, clearly separated from the first sound (S<sub>1</sub>). Slight systolic inorganic murmur (Sm). Second sound S<sub>2</sub>, third sound S<sub>3</sub>. Space P-R = 0.18 sec. Space P-G = 0.04 sec. Serious anemia of grave clinical import. Subsequently cured by liver therapy. Disappearance of G and of S<sub>3</sub>.

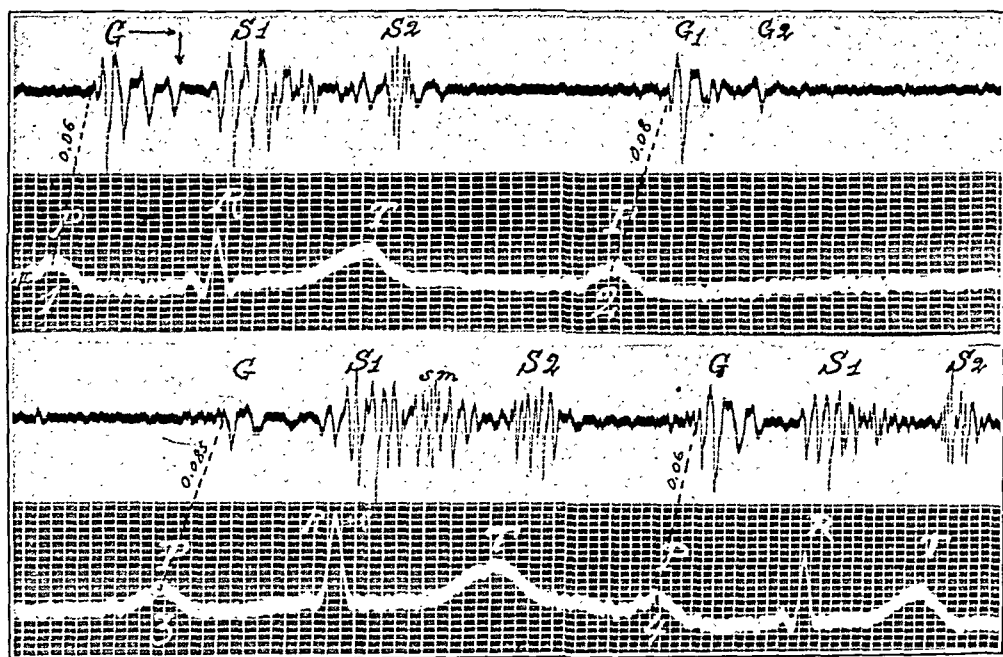


Fig. 7.—Auriculoventricular block produced in a case of hypertension by compression of the carotid (the same patient as in Fig. 3). Phonocardiogram and EKG (owing to its length the tracing is divided into two parts which should be read in succession). The isolated auricular systole (No. 2) gives rise to a double sound G<sub>1</sub> and G<sub>2</sub>. The auricular contraction No. 1 produces the sound G which is single, but its total length equals that of the two sounds G<sub>1</sub> and G<sub>2</sub> combined. At the end of the long diastolic pause the sound G is weakened and modified (No. 3). Space P-G No. 1 = 0.06, No. 2 = 0.08, No. 3 = 0.085, No. 4 = 0.06 sec.

nine years old suffering from pernicious anemia. This patient had at the same time gallop rhythm and an exaggerated third heart sound (four-time rhythm of Laubry and Routier). It is useless to insist here on this third heart sound. We shall confine our attention principally to the distinctness and intensity of the added auricular sound.

BLOCK GALLOP IN STOKES-ADAMS DISEASE

In Stokes-Adams disease, auricular sounds are generally imperceptible, but in almost all cases these auricular sounds appear on the tracings. The tracings of Lewis, Groedel, Selenin and Vogelsson support this statement. The tracing of Fig. 7 represents the heart-block brought about by the compression of the carotid in the case of hypertension as depicted in Fig. 3. Here the oscillations of phonocardiogram of the isolated auricular systole comprise two crests  $G_1$  and  $G_2$ . In fact, in almost all cases the auricular sounds in heart-block are doubled. We ourselves<sup>17</sup> have already published two cases where this doubling was even more striking. W. Reid,<sup>19</sup> Groedel, Selenin and Vogelsson have also recorded similar cases. As to why the auricular sound is double in heart-block and single in presystolic gallop, we cannot say. But the fact exists, and our tracing, Fig. 7, illustrates this point.

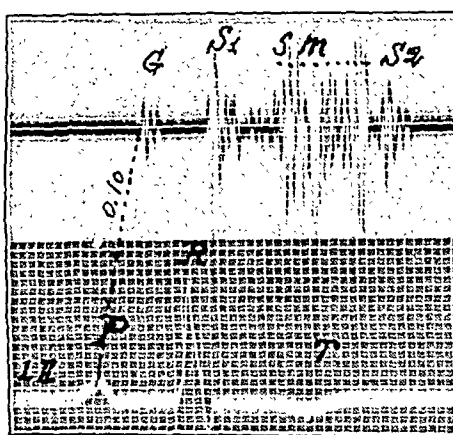


Fig. 8.

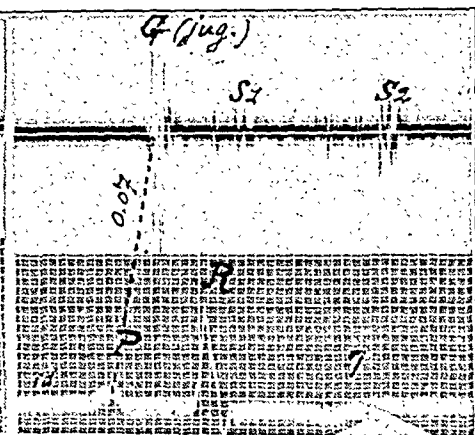


Fig. 9.

Figs. 8 and 9.—Perforation of the interventricular septum. Absence of cardiac compensation. X-ray shadow of the heart increased in all its diameters. Fig. 8, to the left, is the record at the aortic area.  $G$  is the presystolic sound,  $S_1$  is the first sound,  $Sm$  is the systolic murmur, and  $S_2$  the second sound. Space  $P-G = 0.10$ . On the right, Fig. 9 is a record of events above the left collar bone.  $G$  represents the intense presystolic sound,  $S_1$  the feebly transmitted first sound,  $S_2$  the second sound. Space  $P-G = 0.07$  sec.

The wave  $P$  (No. 1) preceding the ventricular systole produces a single sound  $G$ , while the corresponding sound is doubled in the auricular systole No. 2. It should be noticed that the total length of the double sound is the same as that of the single sound and that reduplication is due simply to the attenuation of intervening oscillations. In one case only of presystolic gallop have we observed a double presystolic  $G$ -wave.

AURICULAR SOUNDS IN EXTRASYSTOLIC ARRHYTHMIA

In the case of two normal subjects exhibiting ventricular extrasystoles we have observed on the tracings acoustic waves corresponding to a  $P$ -wave coming after the ventricular extrasystole. The only interest attached to these cases is the consideration of the space  $P-G$  with which we shall deal later on.



## GALLOP RHYTHM AND CONGENITAL DISEASE OF THE HEART

This paragraph deals with an isolated case, that of a young girl twenty years old with a perforation of the ventricular septum, but showing no sign of cardiac decompensation. Auscultation revealed the presence of the usual loud systolic murmur in such a cardiac lesion. In addition, over the whole precardiac region one heard a loud presystolic sound well separated from the systolic sound with its maximum intensity in the aortic area. This sound was also perceptible with extraordinary intensity above the left collar bone. The added sound in this case interests us only from the point of view of auricular etiology, and it cannot be included in a clinical survey of gallop rhythm. Figs. 8 and 9 show the record of this presystolic sound in the aortic area and in the jugular region. Its auricular origin cannot be doubted in view of its relationships with the P-wave. It should be noticed that the space between P and G is 0.03 sec. shorter in the jugular than in the aortic area.

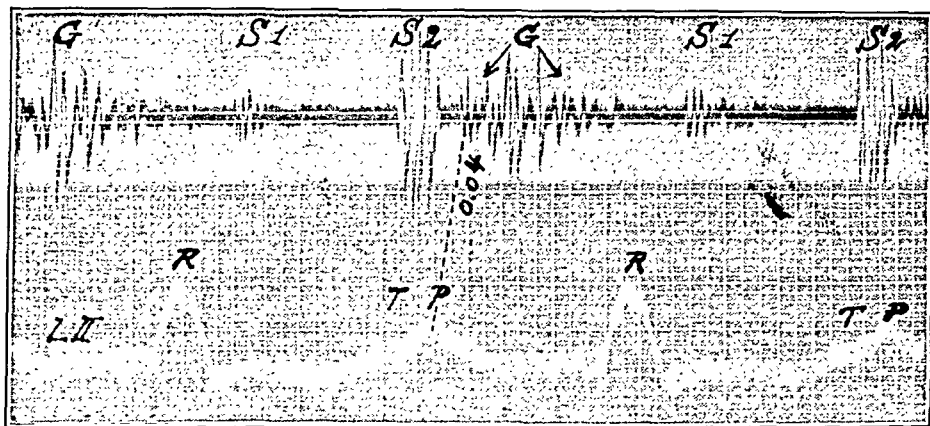


Fig. 10.—Hypertension, nephritis, uremia. Acquired syphilis at the age of twenty-four years. Male, forty-two years, Wassermann positive. Phonocardiogram mid-cardiac and EKG. Diastolic gallop rhythm. Space P-R = 0.30. Added protodiastolic sound G. Dull first heart sound S<sub>1</sub>, accentuated second sound S<sub>2</sub>. Space P-G = 0.04. Clinical conditions very serious. Patient died eight days after the taking of tracing.

## MITRAL STENOSIS AND GALLOP RHYTHM

The anatomical nature of mitral stenosis seems to exclude the production of gallop rhythm. It is difficult to see how the auricular blood wave could give rise to a murmur and a sound at the same time. Several observations, however, among which we must mention the one recorded by Conner, seem to throw doubt on this idea. We ourselves have on two occasions observed an intense additional sound in mitral stenosis. The two cases were very different. In the one case the added sound was certainly due to a third heart sound. In the other case, the added sound was perceptible only in the tricuspid area, while at the apex there was a feeble presystolic murmur. In this latter case we are probably in the presence of gallop rhythm of right ventricular origin. This view is supported by the enormous hypertrophy of the right ventricle.

We cannot discuss with much detail the cases of diastolic gallop caused

by prolongation of the P-R interval, since we have only two tracings at our disposal.

Fig. 10 is an example of diastolic gallop. The auricular sound G is nearer the second sound than the first on account of the prolongation of the conduction time and of the shortness of the space P-G which lasts only 0.04 sec.

The different tracings of gallop rhythm discussed hitherto present certain differences. These differences concern principally the distinctness and the quality of the rhythm which in their turn depend on the intensity and the acoustic qualities of the additional auricular sound. At first sight no general clinical conclusion can be drawn from them. On the other hand the chronological study of the relationships of the wave P with the sound G seems to us to be of great importance in prognosis.

#### DISTINCTNESS OF GALLOP RHYTHM

The distinctness depends on the intensity of the added sound and the silent space which separates it from the first sound. This space itself is determined by several important factors:

(a) The duration of the sound G. If the sound G is short, it is more likely to be separated from the first sound (cf. Fig. 5).

(b) P-R interval. The prolongation of conduction time throws back into the diastole the sound G, which becomes quite distinct from the first sound, even though it be weak.

(c) P-G interval. As we shall see later on, this interval varies considerably. The longer it is, the nearer the sound G approaches the first sound, and the more indistinct it becomes.

(d) R-S<sub>1</sub> interval. In a few cases, the first heart sound begins several hundredths of a second after the R-wave, which fact separates it more clearly from sound G. Differences in the interval R-S<sub>1</sub> depend also on the area at which the registration is made.

One should be cautious in drawing clinical conclusions from the distinctness of the rhythm, since this depends upon different factors. In diastolic gallop rhythms, Gallavardin<sup>7</sup> has already drawn attention to variations of the interval R-S<sub>1</sub> which are susceptible of modifying this rhythm.

One can, however, conclude that a gallop rhythm whose first two sounds are clearly separated, and where the P-R interval shows no prolongation, is almost always of bad prognosis (cf. further P-G interval).

#### INTENSITY OF ADDED SOUND G

This varies with the auscultation areas and with the respiration phases in certain cases. In general, the gallop rhythm of hypotension is more intense than that of hypertension.

In one case of a patient with hypertension but whose clinical condition was not serious, the inhalation of amyl nitrite doubled the in-

tensity of the sound G, without notably increasing the heart rate. In the same case pressure exercised on the carotid caused the sound G to disappear almost entirely, while the heart rate dropped only from 78 to 74.

In two cases of auriculoventricular block the auricular sounds were more intense when they occurred at the end of diastole. While in the case of the induced block of Fig. 7, the sound G is sensibly diminished at the end of the long diastolic pause. In another similar case after a block temporarily induced we noticed on the resumption of normal rhythm a considerable weakening of the sound G during a period covering more than thirty systoles.

Ventricular extrasystoles altering the regularity of the rhythm also change momentarily the intensity of the auricular sounds which follow the compensatory pause. In many cases the gallop disappears after an extrasystole, but in one case it was reinforced.

One cannot therefore draw any conclusion as to the prognosis from the intensity of the additional sound.

#### tone of the added sound

The tone differs according to the case. In hypertension it varies between 25 and 50 double vibrations per second. In our five observations of hypotension it oscillates between 40 and 58. In this latter case therefore, it is higher and this fact would explain the distinctness of gallop rhythm in the cases of hypotension.

The G sounds of tone below 30 vibrations are difficult to perceive by auscultation, but they are often perceived on palpation.

#### DURATION OF THE ADDED SOUND

This varies from 0.04 sec. to 0.15 sec. A long G sound is generally intense, but the contrary is also sometimes observed. The duration of the G sound is no indication of the seriousness of the case.

We have not noticed any relationship between the form of G and that of P.

#### P-G INTERVAL, OR TIME BETWEEN THE P-WAVE AND THE AURICULAR SOUND

This time is measured from the middle of the P-wave to the beginning of the sound G. Figures taken on our tracings lead us to formulate two important laws.

*First law: The duration of the P-G interval is an index of the seriousness of the affection.*

This law applies to all the cases of auricular sounds which we have presented here, independent of their variety, whether the nature of the gallop be presystolic or diastolic; whether it occur in cases of block, mitral stenosis, congenital affections, etc. The duration of the P-G interval varies from  $-0.02$  to  $0.14$  sec. according to the case and is completely independent of the intensity of the sound G.

The maximum variation of the P-G interval is 0.01 sec. according to the area at which the tracing is made. Rhythmic troubles, such as extrasystoles, induced block, bradycardia or tachycardia, never modify it by more than 0.02 sec.

Whenever the interval P-G is less than 0.05 sec., prognosis is very bad. When it is greater than 0.05 sec., cardiac decompensation is less accentuated and a longer survival is probable. The observations presented in

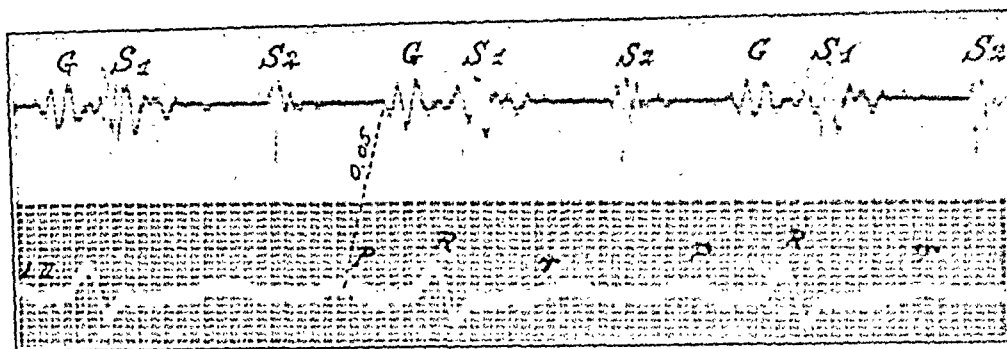


Fig. 11.—Myocarditis with rapid evolution. Tracings recorded January 6. P-G interval 0.05 sec., arterial tension 105/70. EKG, low voltage in three leads.

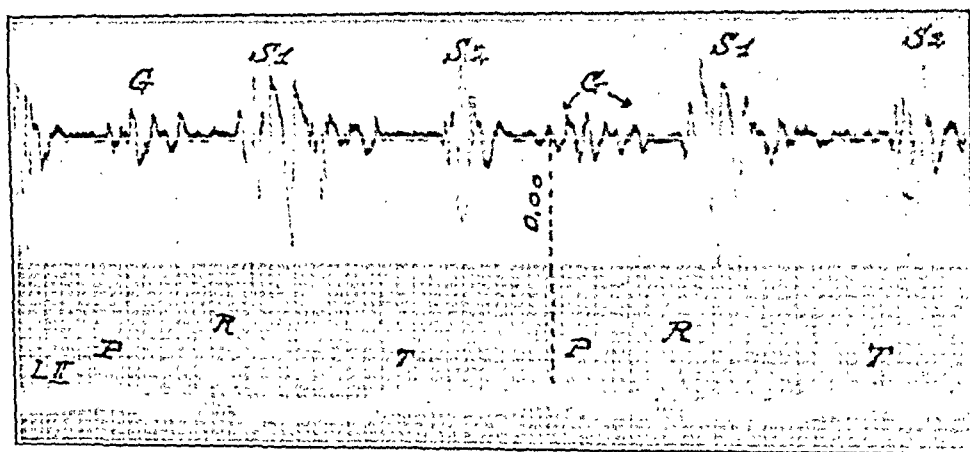


Fig. 12.—The same patient as in Fig. 11. Clinical condition much worse. Tracings made January 12. Gallop rhythm distinct as before. P-G interval = 0.00.

this communication include one exception only to this law. To illustrate our first law, we shall now give a brief summary of our cases:

*P-G interval less than 0.05 sec.* Twelve very serious cases, in ten of which the patients died within two months, and two survived. Of the survivals one was a case of pernicious anemia treated and cured by liver extract, the other case was one of myocarditis whose condition improved.

*P-G interval greater than 0.05 sec.* Twenty cases in which cardiac decompensation was not far advanced and in which the clinical condition gave reason to hope for a reasonably long survival. In this group is included the single exception to which we have above referred—one case of serious myocarditis.

*Second law: The P-G interval varies in proportion to the amelioration or the aggravation of the case during its evolution.*

For example the condition of a patient with gallop rhythm whose P-G interval measures 0.06 sec., might become worse and the interval P-G then becomes less, or on the other hand the condition of the patient might improve and the P-G interval then becomes greater than 0.06 sec. In certain rare cases a patient whose clinical condition is very serious and whose P-G interval measures 0.03 sec. might have a temporary improvement on a suitable medical treatment, and in that case the interval P-G would increase to 0.05 sec. or more.

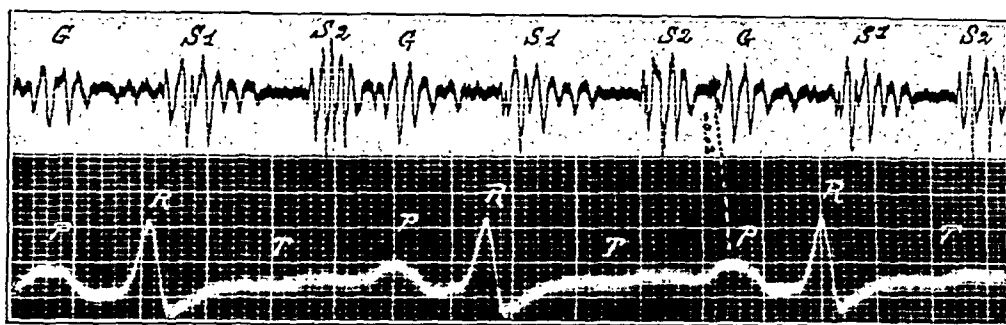


Fig. 13.—Myocarditis. Male, forty-eight years old, alcoholic, Wassermann negative. Blood urea 0.06 per cent. Albuminuria 0.05 per cent. X-ray examination showed the heart sensibly increased in size especially the left ventricle. Tracing taken June 8, 1931, during a serious attack of decompensation. Diastolic gallop rhythm. P-G interval 0.02 sec. decompensation.

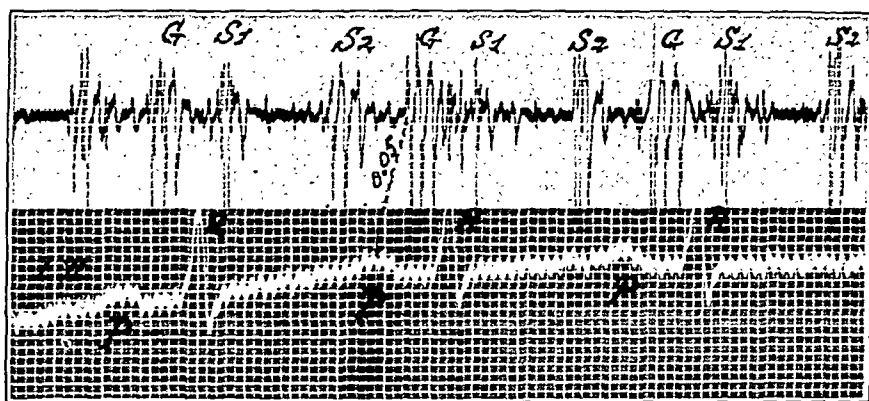


Fig. 14.—Same patient as in Fig. 13. Tracings taken July 13. Considerable clinical amelioration in progress. Gallop rhythm still distinct. P-G interval 0.05 sec.

We shall cite two typical examples of the variations in the length of the P-G interval during the evolution of the disease.

The first example is that of a man forty-four years old, with fibrosis of the myocardium, whose decline was extraordinarily rapid. Hardly four weeks elapsed between the appearance of the first serious symptoms of cardiac decompensation and death. He had rheumatic fever at the age of fourteen, diphtheria at twenty-seven years, no history of syphilis. The first signs of cardiac deficiency appeared in November, 1930. An attack of angina pectoris occurred at the end of December. He had an arterial tension of 170/90. In the beginning of January, 1931, he had acute pain across the chest with intense dyspnea. Auscultation revealed a distinct gallop rhythm. The patient became worse and died January 16. Post-mortem findings by Prof. Askanazy showed the weight of the heart to be 620 gm. There were traces of a previous pericarditis; the valves were intact, and the muscle was much hypertrophied. In the substance of the myocardium appeared large white patches of dif-

fuse myocarditis. The coronary arteries were patent, with slight sclerosis especially at their aortic origin. The four cavities were dilated.

The phonogram tracings taken ten and four days before death are shown in Figs. 11 and 12 respectively. In six days the P-G interval decreased from 0.05 sec. to 0.

The other case deals with a man forty-eight years old, suffering from myocarditis. On entering the hospital his cardiac symptoms were so serious that a fatal issue was supposed to be a question of hours. Diastolic gallop rhythm, easily palpated and clearly audible, was in evidence (Fig. 13). Arterial tension 165/150 mm.

Under the influence of venesection, ouabian parenterally, and subsequently the use of insulin and glucose, the patient gradually improved and after five weeks he could walk a little. It was at this time that the second tracing (Fig. 14) was taken.

On the tracing taken June 8, the P-G interval is negative and measures  $-0.02$  sec. The very early appearance of gallop in relationship to P explains the diastolic appreciation of this gallop, in spite of the fact that the P-R interval is only 0.19 sec. in duration. The second tracing shows the gallop rhythm still distinct, but the P-G interval measures then 0.05 sec. This figure, although still indicating reserve in prognosis, reflects the extraordinary amelioration which took place during five weeks.

#### CONCLUSIONS AS TO THE MECHANISM OF GALLOP RHYTHM

The auriculoventricular mechanism is confirmed by the phonograms. The origin of the added sound can no longer be doubted. The sound is perceptible only in the ventricular area and not in the auricular. Its origin is not therefore due to the muscular contraction of the auricles. It is generally admitted that the hypotonicity of the failing myocardium causes the ventricle to dilate suddenly and loudly under the influence of the auricular blood wave.

How is one to interpret the variations of the P-G interval? This is not an easy question to answer. The two principal factors in the production of gallop rhythm are the auricular contraction on one hand and the ventricular hypotonicity on the other. It is reasonable to suppose that the modifications in the P-G interval are the result of variations in these two factors during the evolution of the disease.

If the ventricular hypotonicity increases with the gravity of the case, one might suppose that the auricular wave-shock would cause the ventricle to expand more easily and the G sound would be more quickly perceived.

On the other hand, it is possible that the volume of the auricular contraction is greater when cardiac decompensation is far advanced on account of venous stasis. If this possibility be borne in mind, the quick transmission of the auricular G sound can be plausibly accounted for.

Against the argument based on the hypotonicity of the ventricle, one can say that this latter should retard the transmission of the auricular blood wave, and *ipso facto* the sound.

In our opinion more importance should be attached to the increased volume of the auricular blood-wave in advanced decompensation. We do not wish, however, to deny the importance of ventricular hypotonicity in the production of the sound; this fact is no longer questioned.

Our conclusions upon this point are the following:

Muscular hypotonicity of the ventricle is necessary for the production of gallop rhythm. This factor alone, however, is not sufficient to explain all the phenomena of gallop rhythm as indicated in our tracings. Simple auscultation does not reveal these phenomena. From the study of our tracings we are of the opinion that the variations in the P-G interval arise from the variations in the force and volume of the auricular wave, while the hypotonicity regulates the production and the acoustic quality of the sound.

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## LOCALIZATION OF EXPERIMENTAL VENTRICULAR MYOCARDIAL LESIONS BY THE ELECTROCARDIOGRAM

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**E**FFORTS to localize ventricular myocardial lesions by means of the electrocardiogram were given impetus by the observations of Herick<sup>1</sup> and later of Pardee<sup>2</sup> on the electrocardiographic changes following proven coronary thrombosis in man. Previously, Smith<sup>3</sup> had described characteristic alterations in the T-wave and R-T segment after ligation of branches of the coronary arteries in dogs. Parkinson and Bedford,<sup>4</sup> in an admirable paper, described and classified the forms of the R-T segment deviations and T-wave changes in myocardial infarction. They found that the R-T deviation was best seen in either Lead I or III, an R-T elevation in Lead I being associated with an S-T depression in Lead III, and vice versa. They classified all curves which possessed the former features (i. e., R-T elevation in Lead I and S-T depression in Lead III) as T<sub>1</sub> type, and those exhibiting the latter (i. e., R-T elevation in Lead III and S-T depression in Lead I) as T<sub>3</sub> type. They found that some of their tracings showed an R-T deviation in a single lead, either I or III, without significant changes in the other two, or in combined Leads I and II or II and III with no alteration of the remaining lead. However, they considered such findings sufficient to warrant the inclusion of these cases in the above classification. They also pointed out that when the R-T deviation was considerable the T-wave, strictly speaking, was not evident; such curves approximated to the monophasic rather than the diphasic type. Definite T-waves became apparent before the R-T segment completely returned to the isoelectric plane, in which case the direction of the apex of T was constantly opposed to the direction of deviation of the R-T segment. Parkinson and Bedford concluded that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches which produces characteristic T-wave changes," and agreed with Smith<sup>5</sup> that the relation of the infarct to the apex was the important factor in determining modification of the electrocardiogram.

Barnes and Whitten,<sup>6</sup> observing the exact site of infarction at necropsy in a series of cases in which a coronary T-wave or alteration in the R-T interval had occurred, attempted to correlate the site of infarction, the blood supply, as from the right or left coronary artery, and the R-T and T-wave deviations, as classified by Parkinson and Bedford.

Recently, Barnes and Mann,<sup>7</sup> in a preliminary report, have stated that ligation of branches of the right and left coronary arteries in dogs

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resulted in changes of the RS-T segment closely similar to those produced by occlusion of the corresponding branches in man.

In this investigation a study has been made of the R-T segment and T-wave alterations following the production of definitely localized myocardial lesions, the localization of which has been related to the electrocardiographic classification of Parkinson and Bedford.

#### METHOD

An electric cautery was applied to the heart in order to produce a lesion simulating that of myocardial infarction. To facilitate the interpretation of results the ventricular wall was arbitrarily divided into the following eight regions: left apex anterior, left base anterior, left apex posterior, left base posterior, right apex anterior, right base anterior, right apex posterior and right base posterior. Thirty-four successful experiments were performed on cats under sodium amytal anesthesia (75 mg. for an adult cat injected intraperitoneally). Needle electrodes were placed under the skin and tied, the control electrocardiogram being taken after this step. Artificial respiration was then established, the chest opened, and the whole heart exposed by slitting the pericardial sac. A second tracing was recorded, the time noted and the cautery applied to one of the above regions until a burn of about  $\frac{1}{2}$  cm. in diameter was produced. The depth of the burned area was extended as far as possible without penetrating the ventricular cavity. If this precaution were taken very little bleeding ensued. The time was noted and a third electrocardiogram recorded. If it showed no change from the normal, the boundaries of the cauterized area were slightly extended. Thereafter, tracings were taken at frequent intervals, and at the completion of the experiment the heart was removed, examined, and preserved in alcohol.

#### RESULTS

In analyzing the results, the classification of Parkinson and Bedford of  $T_1$  and  $T_3$  types has been adopted as a basis. When individual cases do not conform, the differences are stated. One can either describe the electrocardiographic changes produced by a lesion in a particular area or note the areas from which curves of a definite type were obtained. The former method seems preferable, for by this means all the information given by the latter is included and variations from the basic type are more easily presented. All curves which could be classified definitely were of a monophasic type. In a majority of the experiments the electrocardiographic changes which followed cauterization were only transient and a return to normal ensued despite the continued existence of the lesion. The significance of this will be discussed later. In some instances there was present between the monophasic type of curve and the return to normal, a transitional stage in which a diphasic curve was seen, with the terminal deflection resembling the coronary T-wave.

*Left Apex Anterior* (Figs. 1 B, 2 A, 7 A).—Eight successful experiments were performed, in six of which typical  $T_1$  curves were obtained. In two of these (Cats 3, 26) Lead III presented a low take-off of the R-T interval,\* while in the other four (Cats 1, 13, 20, 30) it showed no

\*R-T interval will be used throughout for both the R-T and S-T interval.

TABLE I  
CLASSIFICATION OF ELECTROCARDIOGRAMS ACCORDING TO TYPES

| SITE OF LESION              | CAT NO. | TYPE           |                | DEGREE OF CHANGE | REMARKS  |
|-----------------------------|---------|----------------|----------------|------------------|--|
| <i>Left Apex Anterior</i>   | 1*      | T <sub>1</sub> |                | definite         | R-T elevation in Leads I, II, III of equal magnitude<br>changes not marked                                       |
|                             | 3       | T <sub>1</sub> |                | definite         |  |
|                             | 4       | ?              |                |                  |  |
|                             | 13      | T <sub>1</sub> |                | definite         |  |
|                             | 20      | T <sub>1</sub> |                | definite         |  |
|                             | 26      | T <sub>1</sub> |                | definite         |  |
| <i>Left Base Anterior</i>   | 27      |                | T <sub>3</sub> | definite         | R-T depression in Leads II and III<br><br>R-T depression in Leads I and II                                       |
|                             | 30      | T <sub>1</sub> |                | definite         |  |
|                             | 5       | ?              |                |                  |  |
|                             | 10      | T <sub>1</sub> |                | definite         |  |
|                             | 21      | T <sub>3</sub> |                | slight           |  |
| <i>Left Apex Posterior</i>  | 24      | ?              |                |                  | R-T depression in Leads I and II   |
|                             | 29      | T <sub>1</sub> |                | definite         |  |
|                             | 6       |                | T <sub>3</sub> | definite         |  |
|                             | 22      |                | T <sub>3</sub> | definite         |  |
|                             | 31      |                | T <sub>3</sub> | definite         |  |
| <i>Left Base Posterior</i>  | 34      |                | T <sub>3</sub> | definite         | R-T elevation in the 3 leads most marked in Lead III<br><br>R-T elevation in the 3 leads most marked in Lead III |
|                             | 1*      |                | T <sub>3</sub> | definite         |  |
|                             | 7       |                | T <sub>3</sub> | definite         |  |
|                             | 9       |                | T <sub>3</sub> |                  |  |
|                             | 23      |                | T <sub>3</sub> | definite         |  |
| <i>Right Apex Anterior</i>  | 33      |                | T <sub>3</sub> | definite         | changes not marked<br>changes not marked   |
|                             | 35      |                | T <sub>3</sub> | definite         |  |
|                             | 32      |                | T <sub>3</sub> | definite         |  |
| <i>Right Base Anterior</i>  | 12      |                | T <sub>3</sub> | definite         | no change in any of the leads<br>slight depression in Lead II<br>no change in any of the leads                   |
|                             | 14      |                | T <sub>3</sub> | definite         |  |
|                             | 17      |                | ?              |                  |  |
| <i>Right Apex Posterior</i> | 39      |                |                |                  | changes not marked   |
|                             | 16      |                | T <sub>3</sub> | definite         |  |
|                             | 36      |                | T <sub>3</sub> | definite         |  |
| <i>Right Base Posterior</i> | 40      |                | T <sub>3</sub> | definite         | changes not marked   |
|                             | 15      |                | T <sub>3</sub> | definite         |  |
|                             | 37      |                | T <sub>3</sub> | slight           |  |
|                             | 38      |                | T <sub>3</sub> | definite         |  |

\*In this experiment, a lesion was produced first at the left apex anterior. When the changes induced had disappeared, the left apex posterior was cauterized.

change from normal. In one instance (Cat 4) a monophasic curve of about equal magnitude was produced in the three leads. Cat 27 was an exception to all the other experiments performed at this site in that a typical T<sub>3</sub> tracing was obtained. A later record in this case showed a coronary T-wave.

*Left Base Anterior* (Fig. 2 B).—Five successful experiments were performed, in two of which (Cats 10, 29) the curves obtained were

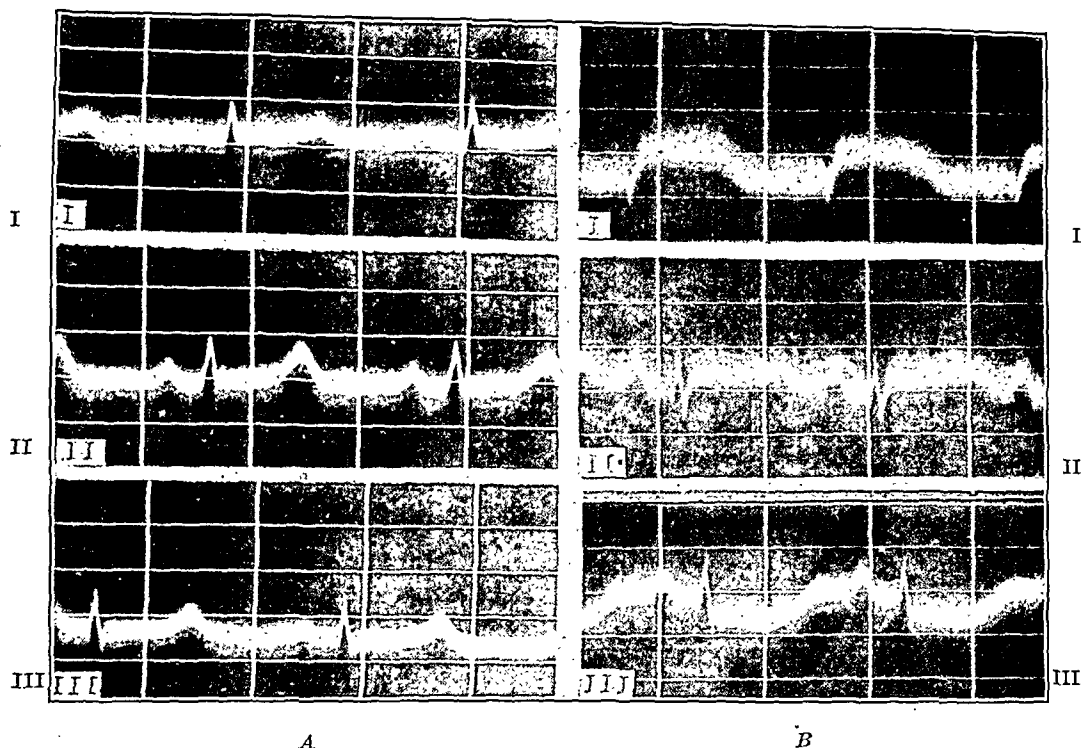


Fig. 1.—A. Normal. B. Lesion at left apex anterior.  $T_1$  type. Marked R-T elevation in Lead I and depression in Lead III. Time  $1/5$  sec. 1 cm. = 1 millivolt.

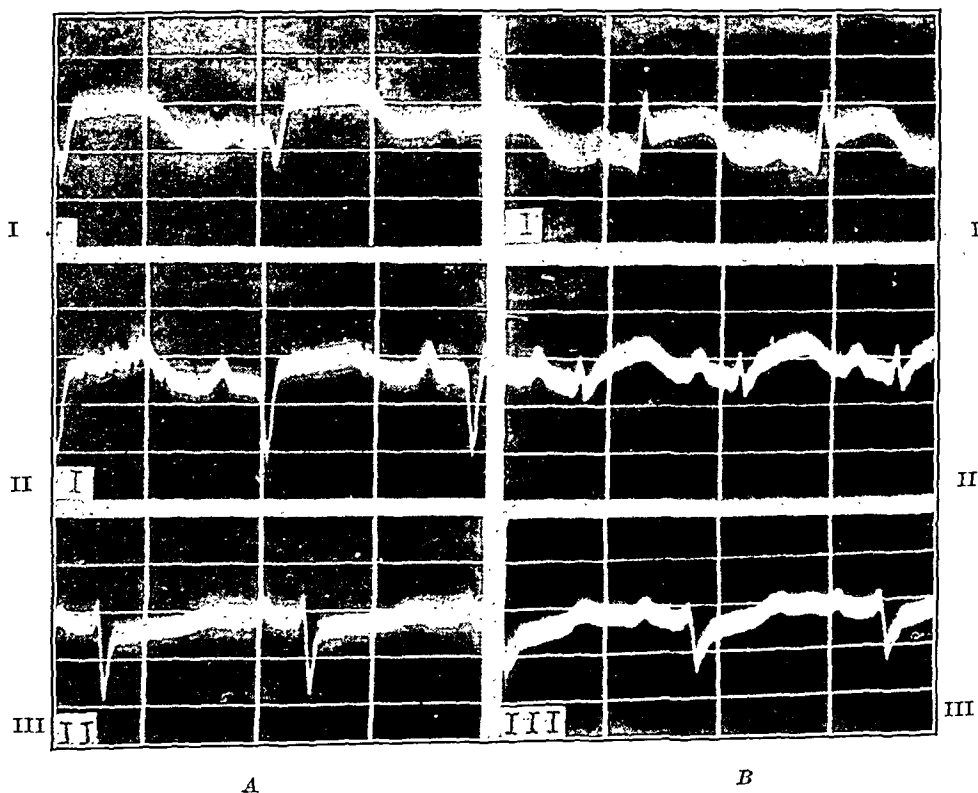


Fig. 2.—A. Lesion at left apex anterior.  $T_1$  type. R-T elevation in Lead I and depression in Lead III. B. Lesion at left base anterior.  $T_1$  type. R-T elevation in Lead I and depression in Lead III.

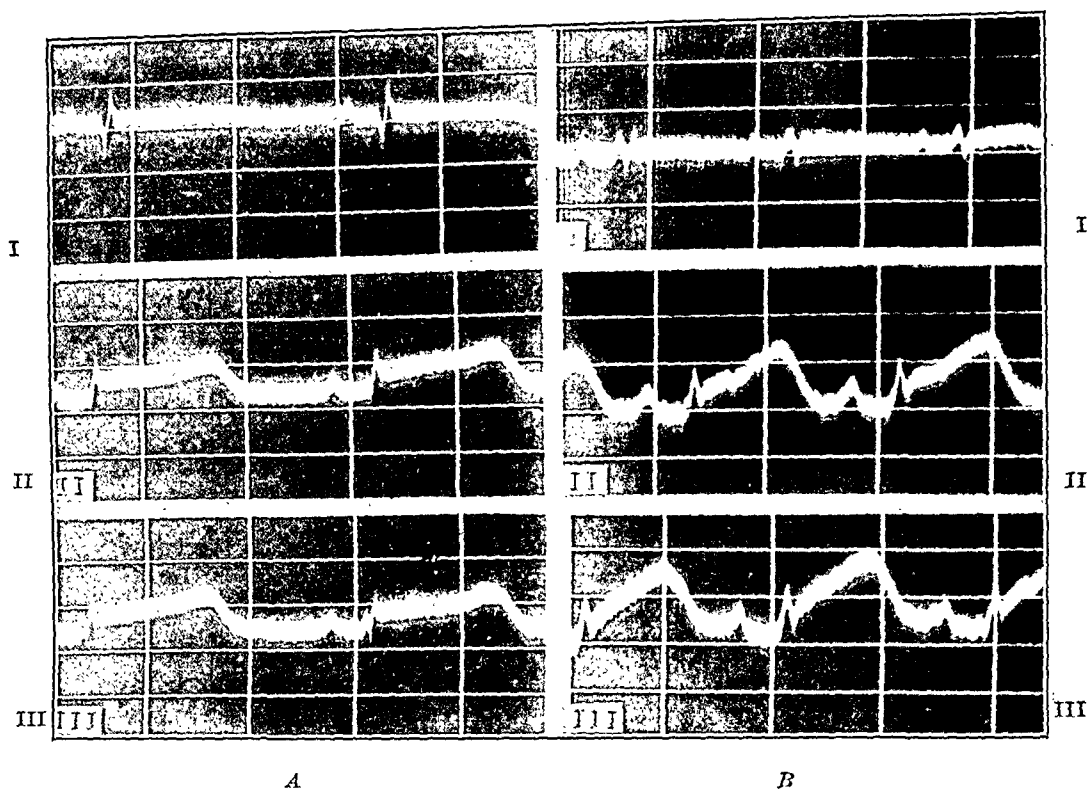


Fig. 3.—A. Lesion at left apex posterior.  $T_3$  type. R-T elevation in Lead III and no change in Lead I. B. Lesion at left base posterior.  $T_3$  type. R-T elevation in Lead III and no change in Lead I.

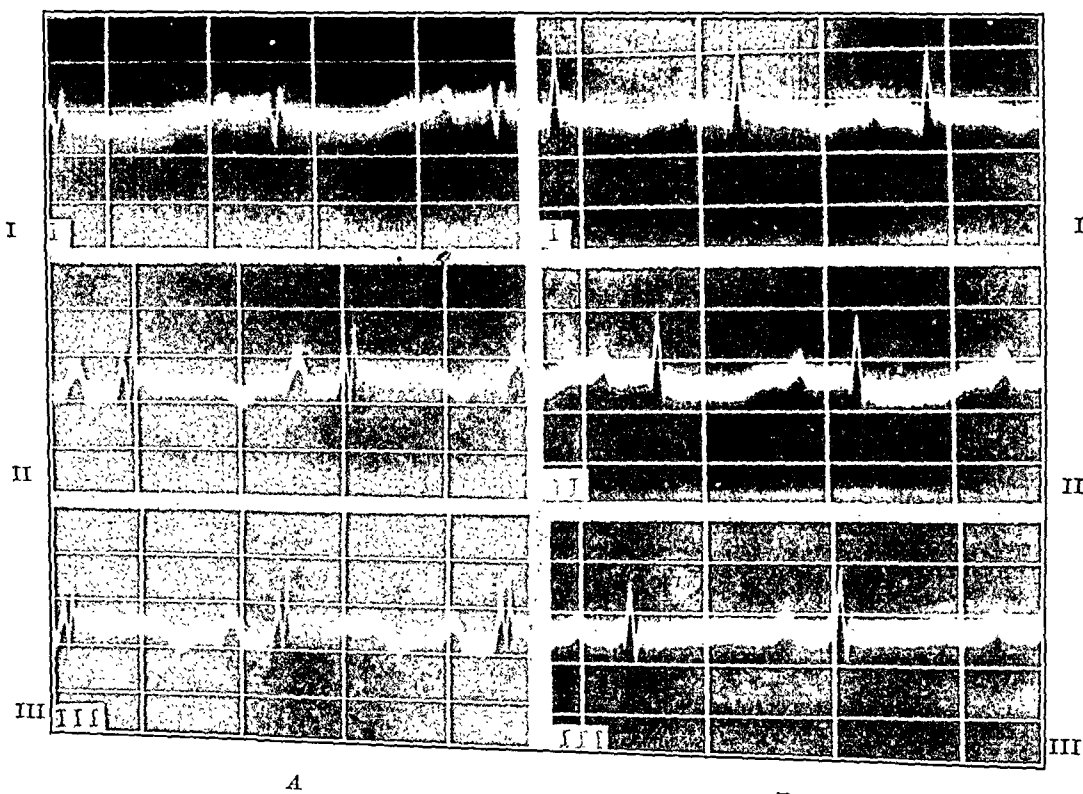


Fig. 4.—A. Lesion at right apex anterior.  $T_3$  type. R-T elevation in Lead III and slight depression in Lead I. B. Lesion at right base anterior. Type undetermined. Slight R-T depression in Lead II.

markedly of the  $T_1$  type, while in a third (Cat 21) there were similar but less pronounced changes. In Lead III, Cat 29 showed no alteration of the R-T segment, Cat 21 a slight depression and Cat 10 a slight elevation which was almost negligible compared to that in the other leads. Cat 24 presented a slight depression of the R-T interval in Leads I and II, and no change in Lead III. In Cat 5 there was a depression in Leads II and III, while Lead I remained unchanged (Fig. 6 B).

*Left Apex Posterior* (Figs. 3 A, 7 B).—Four successful experiments (Cats 6, 22, 31, 34) were performed and in every instance a  $T_3$  type of

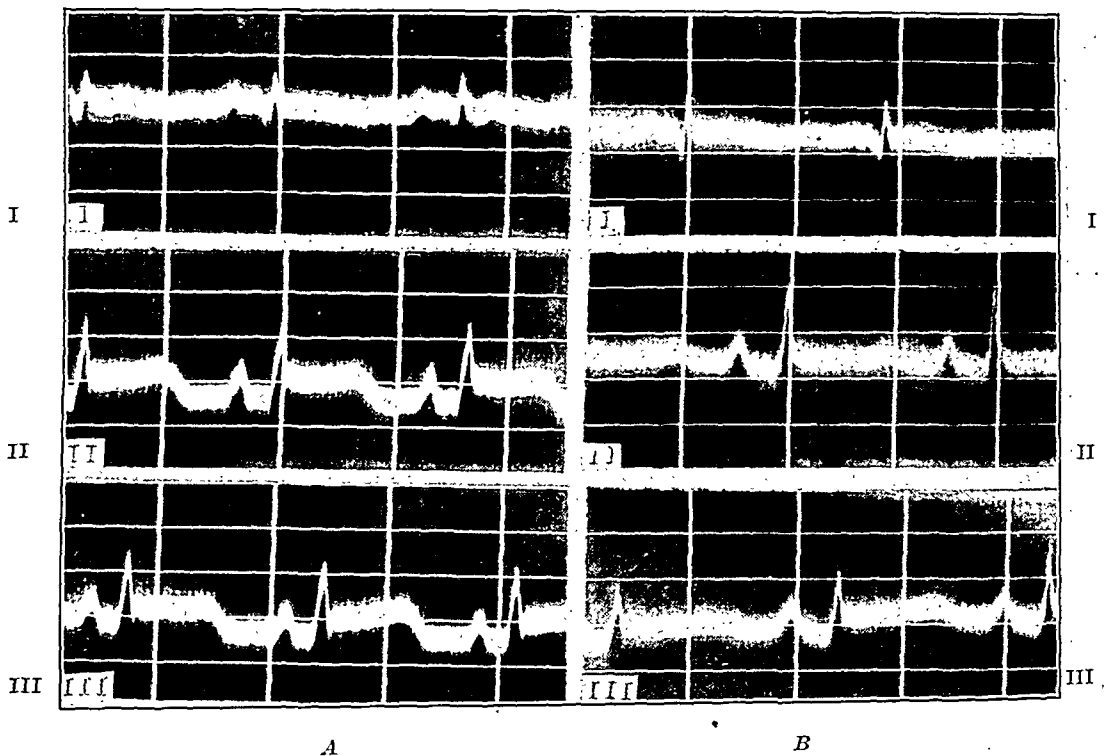


Fig. 5.—A. Lesion at right apex posterior.  $T_3$  type. R-T elevation in Lead III and no change in Lead I. B. Lesion at right base posterior.  $T_3$  type. R-T elevation in Lead III and no change in Lead I

curve was obtained. No change from the normal was observed in Lead I in any of these.

*Left Base Posterior* (Fig. 3 B).—Five successful experiments were performed, in three of which (Cats 7, 23, 35) typical  $T_3$  curves resulted. Lead I in all of these remained unchanged. Cats 9 and 33 presented an elevation of the R-T interval in the three leads but most marked in Lead III (Fig. 6 A).

*Right Apex Anterior* (Fig. 4 A).—Three successful experiments were performed. Cat 12 showed a well marked  $T_3$  type with a slight depression of the R-T interval in Lead I. The other two (Cats 14, 32) presented  $T_3$  types, but the changes produced were much less marked. Lead I in both of these was unaltered.

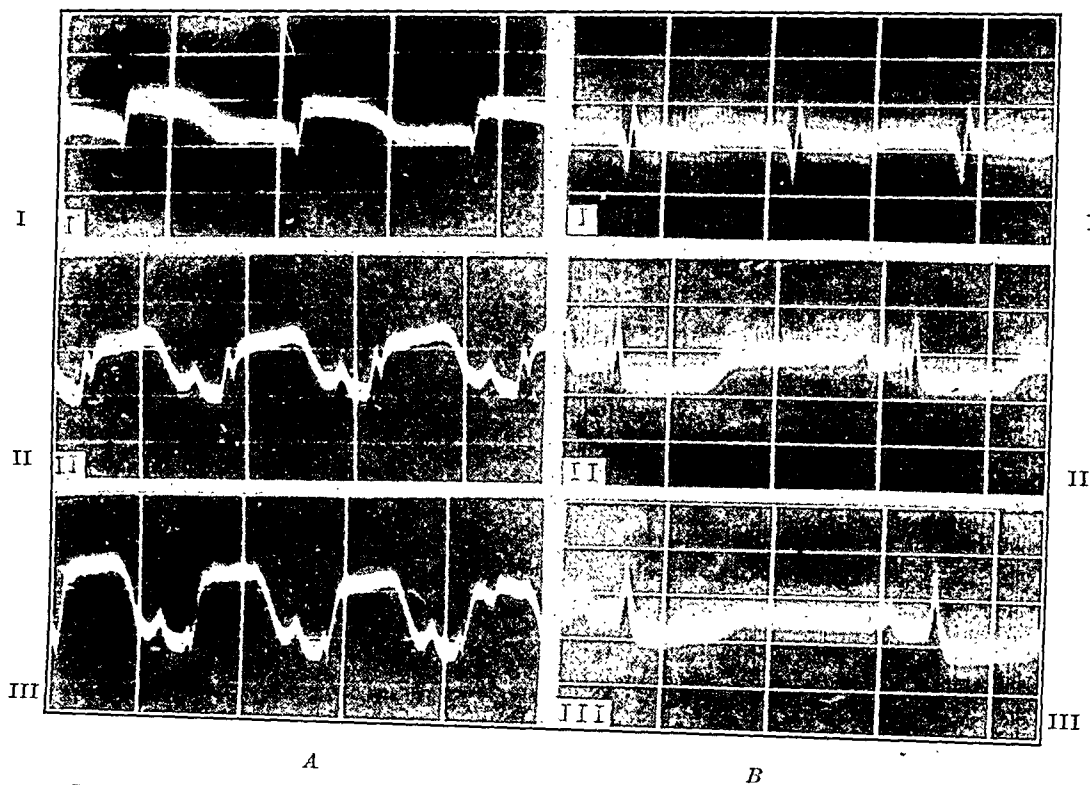


Fig. 6.—Curves presenting unusual characteristics. A. Lesion at left base posterior. R-T elevation in all three leads, most marked in Lead III. B. Lesion at left base anterior. R-T depression in Leads II and III.

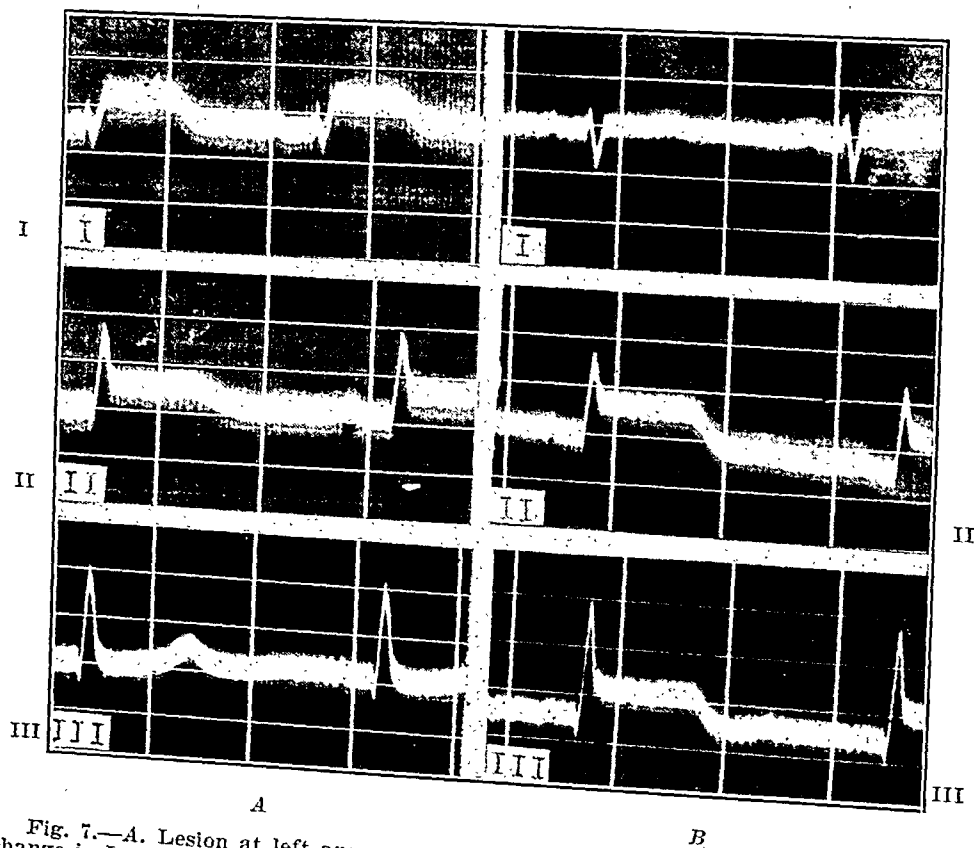


Fig. 7.—A. Lesion at left apex anterior.  $T_1$  type. R-T elevation in Lead I and no change in Lead III. B. Lesion produced at left apex posterior in the same heart after recovery from A.  $T_2$  type. R-T elevation in Lead III and no change in Lead I.

*Right Base Anterior* (Fig. 4 B).—Three successful experiments were performed (Cats 11, 17, 39) none of which showed any marked change in the curves, despite repeated cauterization. However, in one (Cat 17) a slight depression of the R-T interval was observed in Lead II.

*Right Apex Posterior* (Fig. 5 A).—Three successful experiments were performed, in all of which a  $T_3$  type of curve resulted. Two (Cats 16, 40) showed a marked change, while in the other (Cat 36) it was slight but definite. Lead I remained unchanged in two, while in one (Cat 40) it presented a marked depression of the R-T interval.

*Right Base Posterior* (Fig. 5 B).—Three successful experiments were performed (Cats 15, 37, 38) in all of which a  $T_3$  type of curve was produced. Cat 37 showed a slight but definite depression of the R-T segment in Lead I. In none of the curves were the changes as great as had been obtained at the right apex posterior.

#### DISCUSSION

Previous investigators have employed various methods to produce in animals a condition simulating coronary occlusion with subsequent myocardial infarction in the human being. As early as 1862, Panum<sup>8</sup> attempted to obstruct the coronary arteries by injecting a mixture of oil, wax, tallow and lampblack into the aorta, but his work is only of historical interest, since the results were inconclusive. Porter<sup>9</sup> and later Hamburger, Priest and Bettman<sup>10</sup> injected suspensions of lycopodium spores directly into individual coronary arteries. The latter group of investigators, who performed their work on dogs, stated that the subsequent lodgement of these emboli in capillaries and arterioles more nearly approximated the clinical finding of coronary thrombosis than the ligation of larger branches.

A number of workers, Samuelson,<sup>11</sup> Porter,<sup>9</sup> Miller and Matthews,<sup>12</sup> Kahn,<sup>13</sup> Otto,<sup>14, 15, 16</sup> Smith,<sup>3, 5</sup> Feil and his collaborators,<sup>17</sup> Barnes and Mann<sup>7</sup> and others, have utilized ligation or clamping of coronary arteries to produce the desired lesion. Feil and his coworkers were careful to exclude the coronary vein from the ligature, which limited the ischemia to coronary artery occlusion, a precaution not taken by previous investigators. Feil further increased the existing myocardial ischemia by occluding the inferior vena cava at various periods during the experiment.

Several investigators have attempted to inject various chemicals into the myocardium of the ventricles in order to produce results similar to infarction. Eppinger and Rothberger<sup>18</sup> injected a 5 per cent solution of mercuric chloride, but they soon discontinued it because of fear that the absorption of the poison would cause complications, and furthermore, it was difficult to recognize the injected area after the heart was fixed in formalin. Later, they used a 20 per cent solution of silver nitrate and found it served very well; the region affected was clearly seen

macroscopically and well outlined microscopically. Smith<sup>5</sup> employed mercuric chloride and nitric acid, but because he experienced difficulty in limiting the effects of these caustics to definite areas of cardiac muscle, the method was discontinued. The same criticism holds for the procedure of Otto<sup>16</sup> who injected 95 per cent alcohol into the myocardium.

Heat and cold were applied to various parts of the heart by Eppinger and Rothberger<sup>18</sup> and Smith.<sup>5</sup> They sprayed ethyl chloride on the epicardial surface of the heart, Smith also applying small pledgets of cotton, some of which had been soaked in water of 120° F. and others in ice water. But the objection to these procedures is that only a fleeting effect was produced, and since subsequent histological examination revealed no marked change in the region which had been subjected to the heat or cold, it was likewise difficult to make any definite localization.

The advantage of the method used in this work is that lesions similar in location and other respects can be reproduced in a series of experiments. This does not apply to the procedure of ligating coronary vessels, for the blood supply to the ventricles varies, with the result that tying off the corresponding vessel in different hearts will not necessarily cause infarction of precisely similar regions in each case. With the cauterization method there is no fear of constitutional effects as is present in the case of injection of caustics. The lesion produced is permanent and definitely demarcated from the surrounding tissue, in contradistinction to that resulting from the application of heat and cold which is transitory and difficult to recognize either macroscopically or microscopically.

Samojloff,<sup>19</sup> in his interpretation of direct lead curves obtained after pinching or cutting the apex of the frog's heart, inferred that the effect produced was a manifestation of the injury current. In injured muscle, injured-uninjured lead-offs demonstrate a difference of potential, the injured part being "negative" to the uninjured. Upon stimulation of the uninjured portion, the wave of excitation spreading toward the injured end is expressed electrically as a decremental variation of the already existing demarcation current. When injured-uninjured lead-offs are taken from the heart, the electrogram of each ventricular response is a monophasic type of curve substantially similar to that resulting from excitation of a strip of locally injured muscle.

Attracted by the striking resemblance, most authors have explained the so-called coronary type of R-T segment deviation in the electrocardiogram as an expression of the monophasic action current similar to that demonstrated by leading directly from the injured heart. Variations in the form, amplitude and duration of the waves in the indirect derivation as compared with the direct were related to the method of leading off. Craib<sup>20</sup> among others does not accept this view. He states that "clinical variations in the T-wave are not to be compared with monophasic curves experimentally obtained from exposed and partly



injured hearts directly led off from injured and uninjured regions respectively." He considers that the alterations in the electrocardiogram resulting from local myocardial injury depend upon the failure of the injured region to contribute its normal component to the electrical field.

Aside from the respective merits of the above views, the use of the term "monophasic" in this paper requires further modification. Craib<sup>20</sup> has shown that diphasic curves are obtained from injured muscle, cardiac as well as skeletal, if the tissue is surrounded by a large moist conductor. An initial brief positive deflection precedes the relatively prolonged negative variation. According to the doublet hypothesis, the electrical field in the fluids bathing the tissue is determined by the simultaneous presence of an anode and a kathode at the tissue surface arising from a common electromotive source within the tissues, so oriented that during invasion the anode leads while during retreat the kathode leads. The initial positive deflection, therefore, is held to be due to the arrival of the anode under the uninjured lead-off. It is recognized that smooth monophasic curves are not easy to obtain from the mammalian heart even with direct leads. Drury and Brow<sup>21</sup> concluded that only an approximation could be obtained, and Katz<sup>22</sup> discussed the difficulties and reviewed the literature. However, the variations in question are limited to the initial deflections, and our problem is concerned with the end deflections only. Therefore, despite the conflicting views as to the origin of the changes following injury, we have chosen to use as a descriptive term "monophasic type," with which so many readers are familiar, to designate the R-T segment deviations.

Barnes and Whitten<sup>6</sup> in their investigation endeavored to correlate the artery thrombosed, the area infarcted and the electrocardiographic changes produced. They found in the average normal heart that the left coronary artery supplied "the entire anterior surface of the left ventricle, the adjacent third of the anterior surface of the right ventricle, the apex of both ventricles, all of the interventricular septum at the apex, the anterior two-thirds of the septum above that point, and the left half of the posterior surface of the left ventricle." The remainder of the heart was supplied by the right coronary artery. They studied forty-seven cases and found in twenty-one of these in which the electrocardiograms were of the  $T_1$  type, that the infarction occurred in the anterior and apical portions of the left ventricle in the region supplied as a rule by the left coronary artery. In six cases in which  $T_3$  type had been present the infarction was in the posterior part of the left ventricle in the region usually supplied by the right coronary artery. Four cases showed a change, while under observation, from one type to the other. It was found on autopsy in these that two infarcts were present and that the above rule obtained, i. e., if the older infarct were in the anterior part of the left ventricle  $T_1$  type would be present originally while the more recent infarct in the posterior part of the left ventricle caused a shift to the  $T_3$  type and vice versa. In the only instance

in which multiple lesions were carried out in our experiments (Cat 1) we were able to corroborate this finding. The left apex anterior was cauterized and a typical  $T_1$  tracing was obtained. After a time the electrocardiogram returned to normal and then a lesion was produced at the left apex posterior which caused a typical  $T_3$  curve to appear (Fig. 7 A and B). In only one of Barnes and Whitten's cases where a  $T_3$  type was obtained was the infarction found to be in the anterior portion of the left ventricle. In four the type of change in the tracings could not be determined while in seven alterations in the conduction system had been induced which obscured the picture. They concluded that "Infarction limited to the anterior portion of the left ventricle, either alone or combined with infarction of the apex, or infarction of the apex alone, produces modification of the R-T segment of type  $T_1$ , whereas infarction of the posterior portion of the left ventricle, with or without infarction of the apex, produces modification of the R-T segment of type  $T_3$ ." They believe that as far as the electrical forces which effect the R-T segment are concerned the left ventricle can be divided into an anterior two-thirds including the apex and a posterior third. Parkinson and Bedford had found that infarction of the right ventricle was rare, a fact which was corroborated by Barnes and Whitten. Bell and Pardee<sup>23</sup> described five cases of their own and seven which Levine<sup>24</sup> had reported and found that the tracings and autopsy results corresponded in the same manner as those of Barnes and Whitten. A case has been described by Bates and Talley<sup>25</sup> and another by Purks<sup>26</sup> in which stab wounds of the chest cut the left anterior descending artery, and in both of these  $T_1$  type of electrocardiogram resulted. Gilchrist and Ritchie<sup>27</sup> in an analysis of their records confirmed the findings of Parkinson and Bedford. However, they were unable to substantiate the views of Barnes and Whitten in a comparison of electrocardiograms and autopsy reports in one case of their own and in cases previously published by other authors.

When one attempts to correlate the R-T deviations with the site of myocardial damage, produced either by coronary occlusion or local injury, the earlier experimental work is inapplicable to the problem in that no electrocardiograms were taken. Likewise, the work of Samojloff<sup>19</sup> and Eppinger and Rothberger<sup>18</sup> can not be considered, as standard leads were not used. On analyzing the earlier work of Smith<sup>3</sup> one finds inconsistency in the type of curve obtained after the ligation of corresponding arteries in a series of dogs. In his later work<sup>5</sup> which included the use of heat and cold, and the injection of nitric acid and mercuric chloride, the results cannot be applied as only Lead II is illustrated and no description of the changes in individual leads is given. Hamburger, Priest and Bettman<sup>10</sup> also obtained inconsistent results. Most of the work of Otto is inapplicable as he used only Lead II or chest leads. In one paper<sup>14</sup> in which standard leads were taken he found that ligation of the second large branch of the left circumflex artery caused

an R-T fusion in Leads I, II and III, or in II and III, while inconstant R-T fusion resulted from the ligation of the left anterior descending branch. He considered that the former supplied the left part of the posterior surface of the left ventricle. However, it is difficult from the description to localize the probable area of damage. He states that ligating the right coronary artery causes S-T depression and fusion. Feil and his coworkers<sup>17</sup> carried out an extensive investigation on dogs which was largely concerned with the problem under discussion. They ligated the left anterior descending artery from which the vein had been separated and found that no characteristic R-T deviation resulted. However, if the blood supply to the heart were further impaired by temporarily ligating the inferior vena cava definite changes appeared. The explanation of Feil that the typical changes are dependent upon a considerable degree of cardiac anoxemia seems to be well founded. It is probable that in the production of our lesions, handling the heart caused general cardiac anoxemia. Feil and his coworkers were unable to substantiate the views of Barnes and Whitten. Although the changes in Lead I showed fair agreement with their thesis, considerable disparity in Leads II and III was present. However, Barnes and Mann,<sup>7</sup> in a later investigation, reported that ligation of the branches of the left coronary artery in the dog resulted in changes in the RS-T segment of the electrocardiogram which are closely similar to those produced in man following obstruction of the anterior descending branch of the left coronary artery, and leading to acute infarction in the anterior and apical portion of the left ventricle. Likewise, the changes of the RS-T segment produced by ligation of branches of the right coronary artery are closely similar to those of occlusion of the right coronary artery in man, and resulting in infarction in the posterior basal portion of the left ventricle.

In all our results a monophasic type of curve was obtained except at the right base anterior. In the great majority of instances the curves could be definitely classified as  $T_1$  or  $T_3$  type. The changes in Lead II resembled those of Lead I in the  $T_1$  type and those of Lead III in the  $T_3$  type. In two instances an elevation of the R-T interval was seen in all leads, but it predominated in Lead III, so that the type could be definitely classified. However, in another the changes appeared to be of equal magnitude in the three leads and it could not be classified. In three experiments, instead of an elevation of the R-T segment the only alteration noted was a depression. The lesions which induced this were at the base of the heart on the anterior surface; two at the left base and one at the right. Of those at the left base one caused a slight depression in Leads I and II, the other in Leads II and III. That at the right base produced a slight depression in Lead II. In some instances in  $T_1$  types the classical picture of a depression in Lead III was obtained, and similarly in Lead I in the  $T_3$  type, but this was not the rule. Parkinson and Bedford found in many of their cases that the typical

changes were not present in all three leads, and did not regard the depression in either Lead I or III a requisite for classification.

When one considers the effect on the electrocardiogram of the location of the lesions, one notes a remarkable degree of constancy. On the anterior surface of the left ventricle, both apex and base, a  $T_1$  type of curve was obtained, except in one instance where cauterization of the apex produced a  $T_3$  type, and in two others where lesions at the base caused a pure depression of the R-T segment in two leads. In one of the latter this depression was present in Leads I and II and in the other in Leads II and III. These curves have not been classified. On the posterior surface of the left ventricle, both apex and base, typical  $T_3$  curves were obtained in every case. It is of some interest to speculate as to the cause of the relative consistency of our results and the inconsistency of those of other workers in their ligation experiments. As has been pointed out, by our method one can produce with considerable degree of accuracy a lesion of approximately the same size, in approximately similar sites in repeated experiments, whereas by ligating a vessel the position and size of the lesion must be modified necessarily by the variations of the blood supply in the individual animals. The site of the lesion produced is of undoubted importance, but the amount of tissue involved has also to be considered. The part of the injured area which at a particular moment is producing the maximal influence on the electrical forces causing the R-T segment might, in a large lesion, vary greatly. When one considers that the left anterior descending branch supplies a variable part of the septum and also sometimes gives branches to the left part of the posterior surface, it is possible that following thrombosis, the portion of the infarct producing the greatest electrical effects might be toward the posterior surface of the heart. This could cause an entirely different picture from that induced by activity towards the anterior surface. It seems unlikely that in all parts of the damaged area an equal degree of change is taking place at the same time.

The changes produced in the right ventricle gave equally definite results. A typical  $T_3$  type of curve was obtained from all sites except the anterior base. On cauterization of the latter site there was no variation from the normal, except in one instance—a slight depression in Lead II. Only at the apex posterior, however, were the changes of the same magnitude as had been found when the left ventricle was cauterized. As noted before, previous observers found greater difficulty in obtaining electrocardiographic effects in lesions of the right ventricle.

Our experimental results substantiate the thesis advanced by Barnes and Whitten from their clinical studies except in one particular, namely that we obtained  $T_3$  type of curves from the left apex posterior. The region cauterized was undoubtedly in the area which they consider to be supplied by the left coronary artery. Whether the discrepancy is due to a different distribution of the blood supply in the cat from the

human, one cannot state at present but studies are in progress to determine the relation of the blood supply to the lesions described. However, it appears most probable, as both Parkinson and Bedford and Barnes and Whitten suggested, that it is the geographical distribution of the lesion rather than any particular blood supply that determines the electrocardiographic changes.

#### SUMMARY

Electrocardiographic changes were studied in relation to the site of damage in thirty-four cats in which localized ventricular myocardial lesions had been produced by the electric cautery. Monophasic type curves were obtained which were classified as of the  $T_1$  and  $T_3$  types of Parkinson and Bedford. With almost complete consistency lesions in similar sites produced the same type of curve. Lesions on the anterior surface of the left ventricle produced curves of the  $T_1$  type, while those on the posterior surface of the left ventricle, including the apex, yielded the  $T_3$  type. All right ventricular sites, except the base anterior in which only a slight change was induced, gave curves of the  $T_3$  type. At the apex posterior alone were the changes comparable in magnitude with those obtained in the left ventricle. Usually the changes produced were marked in two leads. In some the displacement of the R-T segment was oppositely directed in the remaining lead, while in others no significant deviation was observed in this lead. In a few instances an R-T elevation was present in all three leads but as a rule to a greater extent in one lead. In three experiments, in each of which the lesion was located at the base anterior, depression rather than elevation of the R-T segment occurred.

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## COARCTATION OF THE AORTA (ADULT TYPE). A REPORT OF THREE CASES\*

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THREE cases of the adult type of coarctation are reported. Two are new additions to the literature. One has been mentioned previously (Blackford<sup>2</sup>). The latter case is added because of some findings not mentioned in his report.

The history and pathogenesis of coarctation have been so ably reviewed in the literature (Abbott,<sup>1</sup> Blackford<sup>2</sup>) that these features are omitted in this report.

One point which may have a bearing on pathogenesis, particularly for those who still think the condition is of postnatal origin, I wish to mention. Dally<sup>4</sup> in discussing the descent of the diaphragm at birth claims that this descent (contraction) changes the direction of the currents of blood between the auricles and in the ductus arteriosus. He refers to Keith<sup>5</sup> who states: "When the right crus contracts at birth, with the first inspiration, it draws the pulmonary arteries and the fixed margin of the vestibule of the left auricle with it, but the aorta is fixed otherwise and scarcely yields. Hence a decided traction is exercised on the ductus arteriosus, enough I believe to stop the flow of blood from the pulmonary artery to the aorta and turn it into the lung, which at the same time is expanding. . . . Thus the contraction of the right crus, while helping to expand the lung, also closes the foramen ovale and ductus arteriosus."

That this pull exerted at a distance may be one of the jumble of forces acting on the ductus is merely stated. Its influence on coarctation is of course purely speculative. Those who have seen a case of coarctation at the postmortem table can hardly fail to have received the impression that the real cause of coarctation lies in the anomalous redistribution of the primitive arches which go to make up that area of the definitive arch.

The clinical diagnostic criteria for coarctation (adult type) are: (Oppholzer [1848]<sup>6</sup>) (1) differences in pulse volume (palpable) between radial and femoral arteries; absence or minimal pulsation of the abdominal aorta; (2) evidence of arterial collateral circulation on chest and abdomen; (3) aberrant systolic noises on chest (Laubry [1926]<sup>7</sup>); (4) difference in pulse and systolic pressure between arm and leg, the pulse and systolic pressure being higher in the arm (Railsback and Dock [1929]<sup>8</sup>); (5) x-ray evidence of erosion (scalloping) of the ribs.

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## CASE REPORTS

CASE 1.—C. S., aged thirty-two years, male, entered the hospital December 31, 1928, discharged January 16, 1929. The patient was sent in for thyroidectomy. Two basal metabolic rates taken at intervals—the latter, one week before admission—were plus 42.

Present Illness: Onset six years ago—dizziness, shortness of breath, palpitation. Hypertension noted six years ago. He tolerates heat well but suffers from the cold. There has been puffiness of the face and hands. During the last three months he has taken Lugol's solution, minimis 10, three times daily. The patient was referred to surgery because of the request of his physician, and because he had a thrill over the enlarged thyroid, tremor of the fingers on extension of the hands and a history of increased basal rate readings. A hypertension, recorded as 210/134 mm., was noted, and there was also an enlarged heart with a systolic murmur at the apex which was not transmitted.

The family history is unimportant except perhaps for the fact that the mother died of apoplexy (age not stated). The patient is married. His wife and children are well. He has diseased tonsils and cervical adenopathy, also pansinusitis (x-ray).

When seen by Dr. Karl Anderson of the medical staff it was noted that there was a "mass" under the sternum, a to-and-fro extracardiac murmur heard in the back at the angle of the scapula, also several pulsating vessels in the back. The diagnosis was at the time "hypertension," "mass in upper part of the thorax," "hyperthyroidism, questionable." "Operation should be deferred for more accurate study and to obtain a better understanding of extracardiac murmurs." On comparing the radial pulsation with the abdominal and femoral pulsations a striking difference was noted. Further observation of this man revealed, besides the marked pulsation of the arteries of the neck, the visible pulsation of vessels in the back along the vertebral border of the scapula and palpable vessels which pulsated along the intercostal spaces. When this patient became quieter, no cardiac murmurs were audible. A systolic bruit in the neck vessels was heard and there was a postsystolic murmur in both interseapular areas at the level of the second and third thoracic vertebrae. Deformity of the spine (scoliosis) was noted. The mass under the sternum was interpreted as an enlarged vessel off the arch, because retrosternal dullness varied under rest.

Eye grounds—arteriosclerosis, tortuosity of vessels. Kidney function normal. Blood and urine normal. Basal metabolic rate on January 5, plus 4. Electrocardiogram, January 8, 1929—normal complexes, T in Lead I flat.

Blood pressure readings in arms and legs:

|                  |       | <i>Left</i> | <i>Right</i> |
|------------------|-------|-------------|--------------|
| March 3, 1929    | { Arm | 186/108     | 194/112      |
|                  | { Leg | 124/118     | 114/ ?       |
| April 14, 1929   | { Arm | 190/120     | 188/120      |
|                  | { Leg | 120/110     | 120/110      |
| May 24, 1929     | { Arm | 168/102     | 170/102      |
|                  | { Leg | 130/120     | 120/92       |
| January 26, 1930 | { Arm | 208/120     | 198/126      |
|                  | { Leg | 140/120     | 140/118      |
| May 18, 1930     | { Arm | 220/115     | 210/115      |
|                  | { Leg | 140/125     | 140/120      |

Physical findings on January 26, 1930, about one year after discharge from the hospital: Congestion of face and slight cyanosis. Pupils equal, react to light and accommodation. Some visible pulsation of vessels of the neck. Some venous

dilatation. Some asymmetry of thorax—left bulges slightly, moves freely. Some cardiac enlargement. Abdomen is normal. Extremities of good color, veins are quite numerous and visible. Percussion of thorax—clear, no retrosternal dullness found. Patient feels well. Has no roaring in his ears, no headaches. Legs tire when he goes upstairs. Arm and leg pressures noted in table of pressures.

The patient had been working steadily for one year at fairly hard labor in a steel mill.

X-ray Report (Dr. Rigler): January 5, 1929, Ad 6390, Chest and Spine: Fluoroscopic and film examination of the thorax was made. There is a shadow in the superior mediastinum which pulsates slightly. This may be due to a substernal thyroid, but its appearance is not characteristic, and the possibility of its being due to dilated vessels cannot be ruled out. The heart appears to be within normal limits in size, shape and position, but there is a marked distortion of the spine which causes the heart to protrude to the left side. Only the arch and ascending aorta can be fairly visualized. The descending aorta was not well visualized. Plates of the spine reveal multiple deformities, the third and fourth dorsal vertebrae being used together, and the seventh and eighth being very much deformed. Its appearance is characteristic of a congenital lesion, and suggests intercalation. A further study of the spine is advisable. There is a marked deformity of the ribs on the right side, secondary no doubt to the spinal deformity and some scoliosis. Erosion of the ribs along their inferior margins is shown. This is characteristic of dilated pulsating arteries. *Conclusions:* Congenital deformity of spine. Possible substernal thyroid. Possible dilated vessels of neck. Erosions of ribs secondary to dilated intercostal vessels.

January 29, 1930, Ac 864, Chest: Reexamination of the chest and heart with the barium filled esophagus was made. The findings are much the same as last reported. There is little or no distortion of the esophagus except that it is displaced somewhat to the right in the anteroposterior view just below the arch of the aorta. The aorta could not be clearly visualized and suggests an atresia. The distinct erosion of the ribs previously reported is again shown and is due to pulsation of the tortuous intercostal vessels. The deformity of the spine previously reported is again shown. *Conclusions:* Multiple congenital deformities of spine. Erosion of ribs secondary to tortuosities of intercostal arteries. Distortion of esophagus secondary to abnormality of aorta. Enlarged heart, left ventricular type.

Comment: The x-ray report of erosion of the ribs in this man with the correct interpretation of its cause, was made previous to our knowledge of the publication of Railsback and Dock's<sup>s</sup> article. It was decided at the time of the observation to wait for verification of this finding in other cases before calling attention to it. This was neatly done by Railsback and Dock. The syndrome of hyperthyroidism in this case and its appearance in cases of coarctation are discussed subsequently.

CASE 2.—Miss S., aged twenty-one years, patient of Dr. M. W. Alberts, St. Paul.\* The patient was seen in January, 1930. She is a young woman in apparently good health attending the university. She gives a history of having had symptoms of hyperthyroidism five and a half years ago. Thyroidectomy was performed without results. One year later another portion of the thyroid was removed. This improved the patient's nervous symptoms but did not relieve her hypertension which had been present throughout this period. It was then noted and there was a marked

\*We again take occasion to thank Dr. M. W. Albert for his permission to use this case as clinical material and for the opportunity to mention it in this report.



difference in pulsation of the brachial and femoral arteries. The diagnosis of coarctation was made. Since her operation four years ago she has been slightly restricted in her activities.

**Physical Examination:** The patient is a well-nourished, well-developed young woman. There is a full thyroid; the vessels pulsate in the neck but there is no thrill. The heart is not enlarged. All over the chest a systolic bruit is heard. Besides this, cardiac sounds are well heard all over the chest. Along the sternum on the right a systolic murmur is heard which can be traced far down the abdomen to the level of the umbilicus. A similar murmur is heard on the other side of the abdominal wall. Along the right axillary area this systolic murmur is pronounced. In the back, pulsation of intercostals can be made out on palpation from midscapular area to as low as the ninth interspace on both sides. A systolic bruit is heard along the inner margin of the scapula on both sides. The characteristic interscapular systolic noise is not so obvious as in Case 1. There is absence of palpable pulsation in the abdominal aorta and very feeble pulsation of the femorals.

Eye grounds, beginning arteriosclerosis, tortuosity of the vessels. Blood pressure readings:

|               |       | <i>Left</i>       | <i>Right</i> |
|---------------|-------|-------------------|--------------|
| January, 1930 | { Arm | 190/100           | 200/110      |
|               | { Leg | 130/110 difficult | 130/110      |
| In May, 1930  | { Arm | 170/90            | 170/90       |
|               | { Leg | 128/100           | 120/95       |

**X-ray Report:** February 3, 1930, Ae 1023, Chest and Esophagogram (Dr. Rigler): The heart shows only a very slight enlargement, chiefly in the left ventricle. The aorta shows some slight dilatation of the ascending portion, but the arch is small and the descending portion can be very poorly visualized. It can, however, be made out. A definite area of constriction in the aorta cannot be clearly visualized. There is no particular distortion of the esophagus. A definite erosion on the inferior surfaces of the ribs on both sides extending down to the eighth rib posteriorly is clearly made out. This is characteristic of the type of erosion which is clearly made out. This is characteristic of the type of erosion which is due to tortuosities of the intercostal arteries. There is a shadow in the superior mediastinum very ill-defined but suggesting enlarged dilated vessels. *Conclusions:* Slight cardiac enlargement, left ventricular type. Erosion of ribs from pressure of vessels; coarctation of aorta (clinical).

**Comment:** Blackford<sup>2</sup> reported this case, we assume as No. 7. Since he gave no differential blood pressure readings nor mentioned the erosion of the ribs, we have incorporated this data. This is the second case which has come to our notice presenting at some time in the history evidence of a hyperthyroid complex. The possible explanation for this will be given in the discussion.

**CASE 3.**—O. J., aged twenty-three years, admitted March 6, 1930.

**Present Illness:** The patient felt very well until February, 1929, when he developed an inguinal hernia on the right side. This did not trouble him very much so he did light work. The hernia increased during the summer of 1929. He worked in the harvest fields in the fall of 1929. He felt very well when lying on his back and the hernia was reduced. Swelling of the abdomen began in February, 1929. It was gradual and painless. No jaundice was noticed at the time. There was no edema of the ankles, no dyspnea, no cyanosis. He was confined to bed for one month before admission.

**Past History:** His previous health had been good. Apparently he had a normal childhood. He ran and played with the other children. He never was short of breath. The mother noticed that he was usually pale. He never flushed when running. He catches "cold" easily. There have been no headaches, no palpitation. No dyspnea was noticed until six weeks before admission. There is no history of rheumatism. The family history is negative.

**Physical Examination:** On admission there was slight dyspnea, and he was able to lie flat in bed without discomfort. Sclera icteric; slight acrocyanosis. Thorax: Lungs clear; marked enlargement of the heart to the right and left; shape of the heart probably altered by intra-abdominal pressure. A rough systolic thrill was felt at the apex. At the base there was a rough diastolic murmur occupying the whole of diastole evident in the pulmonic area. No other murmurs were noticed. Pulse 41 to 56; occasional extrasystoles. Blood pressure 154/96 mm. Abdomen: Marked ascites; liver down to umbilical level. Liver seems firm, not tender. Spleen not felt. Right inguinal hernia with fluid, easily reducible. Extremities: Reflexes diminished. Slight edema of the legs. Slight cyanosis; radials sclerotic. No clubbing of fingers present.

**Paracentesis on March 7, 1930:** Liver now made out as enlarged, with round hard edge; surface feels granular. Spleen palpable and hard. Lungs clear. Heart: Murmurs have changed; now a rough systolic murmur was heard over the base. Pulsation was made out on vessels of the back particularly along the vertebral borders and in the intercostal spaces. Pulsation of the abdominal aorta was not found. Pulsation of the femorals was very faint. The ascites was controlled by novasural and ammonium chloride. On March 29 the patient was up and about. No edema of the legs. On sitting up, there was systolic retraction at the apex. On palpation a short rough thrill was felt at the apex.

**Paracentesis on April 30, 1930:** Murmurs at base have disappeared. Posteriorly the murmurs persist "postsystolic in time." The point of greatest intensity of this murmur is at the level of the third thoracic spine but can be heard as far down as the seventh spine in both intrascapular spaces. The pulsation of the neck vessels was very forceful but did not have the celerity felt in the other cases of coarctation we have seen. In fact, at times the radial pulse suggests aortic stenosis. There was a systolic retraction in the lower intercostal spaces on the left, in the axillary line. Conjunctivae were slightly yellow.

**Eye Grounds:** "O. D. vessels, particularly the smaller arteries and veins, very tortuous; some change in vessel walls, particularly arteries. O. S. similar to O. D. Tortuosity of small vessels marked." (Dr. Lane.)

**Laboratory:** Blood normal. Icterus index March 11, 1930: 12. Icterus index May 7, 1930: 20. Urine: Urobilin, P. S. P. 80 per cent two hours. Electrocardiogram March 11, 1930: Bradycardia, left bundle-branch block.

Blood pressure ranged from 154/96, 144/86, to normal readings in arms. Leg readings were not obtainable. In September, 1930, readings were obtained in his legs.

|       | <i>Left</i> | <i>Right</i> |
|-------|-------------|--------------|
| { Arm | 140/78      | 140/82       |
| { Leg | 104/90      | 104/90       |

**X-ray Reports:** March 10, 1930, Ae 1894, Six-foot Chest (Dr. Rigler): The heart is greatly enlarged to the right and left with a marked bulging in the region of the conus pulmonalis and considerable enlargement of the left ventricle. The aorta is very poorly visualized, especially in its ascending portion, but even in the descending portion it is very difficult to make out. There is evidence of a marked pulmonary congestion on both sides. The diaphragms are very high. A definite erosion of the inferior surface of the posterior ribs is shown, characteristic of

coarctation of the aorta and due to the enlarged intercostal vessels causing pressure on the ribs. The esophagus shows a definite posterior displacement due to enlargement of the left auricle. Otherwise there is little or no evidence of change.

After evacuation of the fluid from the abdomen, the diaphragm has come down somewhat, and the heart does not appear quite so enlarged but is still massive, and the pulmonary congestion is still very prominent. The findings in the ribs are again shown, and the marked enlargement of the left auricle is definitely shown. The whole appearance suggests a coarctation of the aorta with some other lesion in addition, the appearance suggesting most strongly a marked degree of mitral disease in addition to the aortic disease. There is a marked enlargement of the left ventricle also.

Operations: May 14, 1930. Talma-McCrison operation under spinal anesthesia. Piece of the liver examined microscopically. Report of frozen section: cirrhosis of the liver (Bell). (There was a slight infection of the bronchi following this operation; temperature 102°; leucocytes 15,500.) No pulsation on direct palpation of the aorta reported by the surgeon (Wangensteen) at the time of the operation.

June 13 to 18, tapping of hydrocele.

Discharged June 24, 1930; patient up and about.

Reentered hospital November 4, 1930. Died November 7, 1930.

After the Talma-McCrison operation there was relief of ascites for a brief period. The patient was up and about. The abdomen was tapped at intervals of two and three weeks after leaving the hospital in June. On October 25, 1930, the patient had an attack of weakness, he was conscious of his heart ("pounding fast") and some precordial pain. The attack lasted eight minutes. He has had similar attacks since. These attacks never last more than ten minutes. After each attack the patient feels weak temporarily. Between attacks he does not "know he has a heart." His general health, appetite, sleep, and bowels were normal.

His physical examination on November 4, 1930, revealed no new data. When seen in one of his attacks his heart was very rapid and irregular. There was dyspnea, cyanosis and sweating. Venesection was done in his fatal attack. Two minutes after venesection the patient gasped suddenly, vomited, and his respiration became spasmodic. The heart stopped before respiration. Electrocardiogram some five hours earlier had shown tachycardia, rate 200, possibly nodal in origin.

*Necropsy* (Dr. O'Brien.)—O. J., A 31-1662. The body is that of a young white male, 175 cm. in length, weighing approximately 165 pounds. Nutrition and development are good. No edema or jaundice. The abdomen is distended. The veins over the anterior and lateral chest wall and abdomen are prominent.

The peritoneal cavity is filled with 6000 c.c. of clear straw colored fluid. The liver is firm and extends well below the costal margin.

The pleural cavities are free of adhesions and effusion. The pericardial sac contains approximately 100 c.c. of clear straw colored fluid.

The heart shows generalized enlargement. It weighs 870 grams. It is 20 cm. in width, the thoracic width at this level being 27 cm. All chambers are enlarged, especially on the right. The left ventricular walls vary from 1.5 to 3 cm. The right varies from 1.0 to 2.0 cm. in thickness. The auricular walls are thickened and distended. The mural endocardium is smooth and shows no thrombosis. The valve edges are free and leaflets are thin. The interauricular and interventricular septa are intact. The coronary arteries show slight internal atheromatous deposits, but no interference with the lumina. There are diffuse yellowish deposits in the pulmonary artery, root of the aorta, base of the aortic valve and the aortic leaflet of the mitral valve. The muscle is slightly cloudy but shows no evidence of fibrosis.

The aortic arch rapidly tapers down to a moderate constriction proximal to the left subclavian artery. There is a more marked constriction near the junction

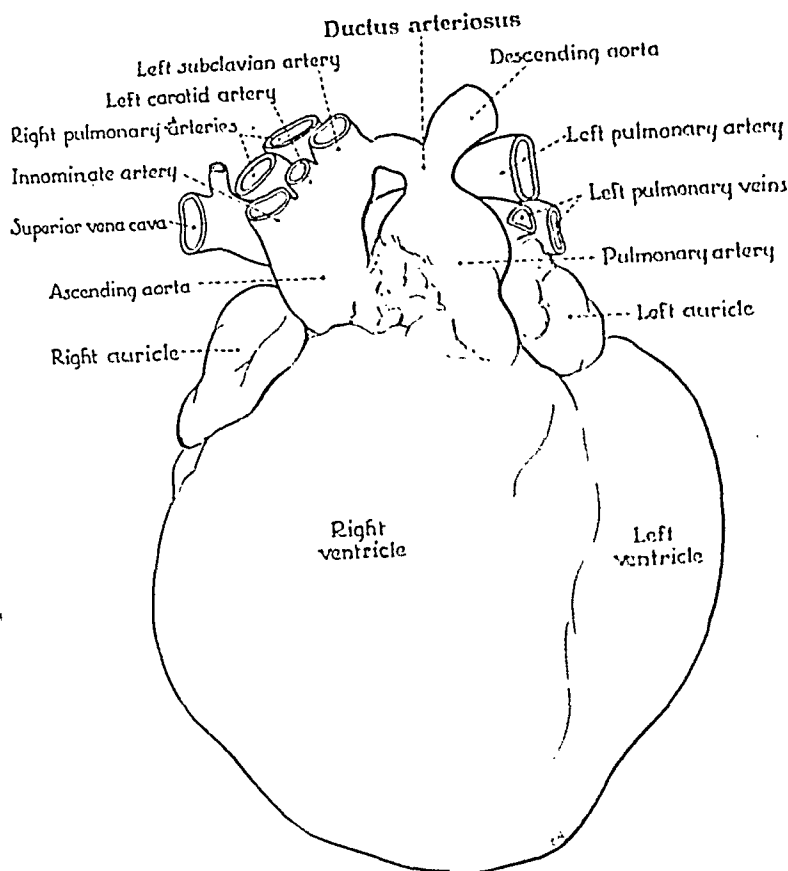


Fig. 1.—Viewed from above and slightly to the left, this drawing is an excellent proportionate outline of the heart and vessels. The arch is somewhat displaced to the left due to fixation. The descending aorta is also distorted by the removal of the specimen from the body and by fixation. The narrowing beyond the left subclavian is marked but does not give an adequate idea of the extent of the atresia because the vessels have not been opened. (See report of the pathologist.)

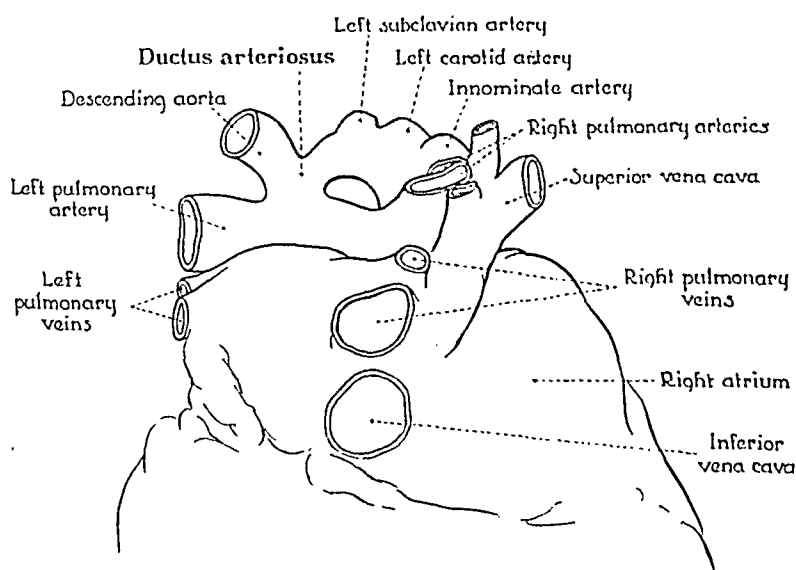


Fig. 2.—Viewed from below and behind. The same distortions of the arch and descending aorta (for similar reasons as in Fig. 1) are noted.

of the arch with the descending portion. The ductus arteriosus is patent and connected with aorta, at the site of the marked constriction. A probe is passed through the ductus arteriosus and passes readily into the descending aorta. It is practically impossible to pass a very fine probe through the distal stricture of the aorta. The descending aorta is smaller than normal. There is a dilatation of the proximal portion of the descending aorta for a distance of 5 cm. Beyond this it is uniformly narrowed, averaging 1 cm. in diameter. The common iliac vessels are smaller than normal but show no other abnormalities. The left carotid is normal in size. The left subclavian artery is dilated and thickened. The innominate artery is distended and has a thin wall. All of the intercostal vessels are markedly dilated, thickened and tortuous. The change is most marked in the first intercostal vessel on the left side. This vessel is approximately the same size as the right carotid artery. Both subclavian arteries are marked dilated. The internal mammary arteries are dilated and tortuous. The axillary arteries are apparently normal in size. The pulmonary artery and conus are markedly dilated. The two pulmonary arteries arise from the posterior superior portion of the distended trunk. The pulmonary vessels show no dilatation nor sclerosis.

The spleen weighs 500 grams and is definitely enlarged. The surface is covered with a diffuse hyaline change. Multiple adhesions between the spleen and stomach and abdominal wall are present. On cut section marked chronic passive congestion is found.

The liver weighs 2,725 grams. Slight hyaline perihepatitis is present, and the surface is roughened due to the liberation of adhesions. The organ is firmer than normal. On cut section marked darkening of the centers of the lobules is seen. There is increased resistance probably due to fibrous tissue deposits. Slight fatty metamorphosis is present throughout.

The right kidney weighs 230 grams and the left 250 grams. The capsules strip without difficulty, and the presenting surface is dark red and hemorrhagic in appearance. There is faint fine pitting over the surface. Section shows the cortices of fairly uniform width.

**Microscopic Examination:** Sections of the heart muscle are normal. No evidence of pulmonary arteriosclerosis is seen. The spleen shows marked chronic passive congestion. The liver presents marked congestion and atrophy of the cords in the liver lobule, especially in the central portion. There is a moderate increase in the portal connective tissue and lymphocytes, presenting the picture of a moderate portal cirrhosis. The kidneys are carefully studied from the standpoint of possible arteriolar sclerosis but none is found.

**Diagnosis:** (1) Coarctation of the aorta. (2) Patent ductus arteriosus. (3) Marked dilatation of the subclavian, carotid, innominate, internal mammary, intercostal and pulmonary arteries. (4) Marked narrowing of the descending aorta and common iliac arteries. (5) Cardiac hypertrophy and dilatation. (6) Chronic passive congestion of all viscera. (7) Ascites. (8) Portal cirrhosis. (9) Vascular adhesions of the stomach, spleen, liver and peritoneal cavity (operation).

#### ASSOCIATED ANOMALIES

Case 1 had a spinal deformity in the thoracic area; the third and fourth ribs were pressed together and the seventh and eighth being much deformed having on the right an intercalated vertebra with an extra rib. This type of somatic deformity is new, using Maude Abbott's<sup>3</sup> report as a criterion.

The aorta in Case 3 certainly suggests aplasia, although the pathologist does not stress this point.

## DISCUSSION

While the clinical criteria are sufficient to make a diagnosis, hemiplegia, or symptoms of hyperthyroidism with increased blood pressure in the young should make one alert as to the possibilities of coarctation. Two of our three cases had evidence of hyperthyroidism. Both Case 1 and Case 2 had definitely increased metabolic rates. In Case 2 the patient had her thyroid operated on twice before she was pronounced normal. Case 1 escaped surgical interference. Rest, with assurance that his condition had been properly diagnosed, and the withdrawal of Lugol's solution reduced the patient's metabolic rate to normal. Lorrigia<sup>9</sup> was the first to mention, and Blackford<sup>2</sup> later noted, hyperthyroidism in connection with this defect. Is the overactivity of the thyroid due to the increased vascularity of the gland? There is an apparent increase of blood flow in the areas above the clavicles. The inferior thyroid comes off the subclavian. The subclavian and its branches are the usual arteries of collateral circulation. That increased blood supply may be a factor in the overactivity of the thyroid in these cases is a reasonable hypothesis. That it may be a factor in other cases reported with this defect is also a legitimate assumption. If this is correct, then ligation of the inferior thyroid may be all that is necessary to relieve the hyperthyroid symptoms in some of these cases.

All three cases, aged respectively nineteen, twenty-two and thirty-one years, had evidence of tortuosity and beginning arteriolar changes in the retina. If, in essential hypertension, arteriolar changes of the vessels in the retina are indicative of arteriolar changes in the vessels leading to the glomeruli in the kidney (Bell), it would be of interest to examine the preglomerular vessels in these cases as they come to the postmortem table. Our single postmortem examination showed no changes in the kidney.

Students of vascular pathology have an important and striking "set up" in these coarctation cases to study the effect of work or tension, plus wear and tear or pulse pressure in the upper part of the body as compared with work or tension in the lower part. It is to be noted that in these three cases while the systolic pressure in the arm is higher than in the leg, the diastolic is the same or even higher in the leg. In other words, there is hypertension in the lower extremities. The observations of Blumgart et al.<sup>10</sup> differ on this point. In one case their readings given for the lower extremity show a lower diastolic pressure than normal. In their second case no diastolic readings in the leg are given. All of our readings were made with a 20 cm. cuff. We found a high normal diastolic (90 mg. of mercury) or above. Blumgart's arteriolar pressures were normal in the legs. Is the high diastolic pressure in the lower portion of the body a compensatory phenomenon to insure adequate arteriolar pressure?

Those interested in the pulse may learn something for or against

their theories as to the factors in its mechanism. The pulse is a distention of the wall of the vessel induced by the increased volume of blood propelled by the systolic force of the heart. In Case 3, during the operation for relief of his portal circulation, the surgeon had an opportunity to feel the aorta in the abdomen. He reported there was no pulsation. I know of no other observation of its kind in coarctation. That this is a constant finding cannot be true. It was usually difficult to get the blood pressure readings in the legs in Case 3, but occasionally they were obtainable. If there was a pulse pressure in the femorals at times, there must have been a pulse in the abdominal aorta at those times. The loss of pulse in Case 3 was due to extreme atresia and the dissipation of the systolic wave in the collaterals. That there was adequate supply of blood flow must be conceded. Not one of these three cases had symptoms of weakness (atrophy or loss of function in the legs. Blumgart et al. suggest from their blood gas studies a low gas reserve in the legs.

All three cases showed the characteristic erosion of the ribs described by Railsback and Dock.<sup>8</sup> This finding has been confirmed by others. The relation of age to the appearance of this defect is pertinently discussed by Fray.<sup>11</sup> If we look on page 385 of *THE AMERICAN HEART JOURNAL*, Vol. 3, 1927-28 (Hamilton and Abbott<sup>3</sup> "Coarctation of the Aorta"), the x-ray plate of the fourteen-year-old boy shows some of the characteristic erosions of the ribs. Realizing the fact that erosion is not an absolute pathognomonic sign, we have studied the esophagogram and its relation to the arch, without any definite results. We do not wholly agree with Fray that the main reliance (roentgenologically speaking) should be placed on the defect in the arch in the left oblique view.

#### SUMMARY

Three cases of adult type of coarctation are reported. The post-mortem findings are given in one case.

Case 1 had a somatic anomaly, involving the thoracic vertebrae. This has not been reported previously in the literature.

The cirrhosis of the liver in Case 3 may have had a basis in the modified blood supply.

The diagnostic importance of x-ray evidences of erosion (scalloping) of the ribs is emphasized.

The findings of increased basal metabolic rate in two cases is mentioned. A possible explanation is suggested for this increase.

Attention is called to the "set up" which these cases afford for the study of vascular problems. The work (tension) in the vessels, plus increased pulse pressure in the head, neck and arms, as contrasted with work (tension) without pulse pressure in the legs is stressed. In the patient who died the arterioles of the eyes (clinical) and kidneys (anatomical) are compared.

# THE ACTION OF ADRENALIN ON PATIENTS WITH COMPLETE HEART-BLOCK AND STOKES-ADAMS SEIZURES

## A COMPARISON OF THE EFFECTS OF THE DRUG ON PATIENTS WITH SYNCOPAL ATTACKS DUE TO STANDSTILL OF THE VENTRICLES AND THOSE DUE TO VENTRICULAR FIBRILLATION\*

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THE purpose of this study was to determine the effect of adrenalin on the heart rate and rhythm of patients with auriculoventricular dissociation subject to Stokes-Adams seizures. It is now definitely established that recurrent syncopal attacks in such patients may be the result of either ventricular slowing and standstill<sup>1</sup> or of the various grades of acceleration of the ventricles leading to transient ventricular fibrillation.<sup>2</sup> While there are now some excellently controlled observations on the action of adrenalin in patients with auriculoventricular dissociation and standstill of the ventricles, both preceding and during the presence of syncope, there are no comparable analyses of the cardiac mechanism following the use of the drug in patients subject to transient periods of ventricular fibrillation. This is of particular importance at the present time, since adrenalin is being prescribed indiscriminately in patients with Stokes-Adams seizures without any knowledge of the mechanism responsible for the attacks.

### REVIEW OF THE EXPERIMENTAL OBSERVATIONS

In studying the distribution of the nerves of the heart, Cullis and Tribe<sup>3</sup> noted an increase in the rate and force of contraction of both the auricles and ventricles in cats and in rabbits in which they injected small doses of adrenalin before and after section of the auriculoventricular bundle.

These findings were subsequently confirmed by Van Egmond,<sup>4</sup> who noted an increase per minute of 15 beats in the ventricular rate and 30 beats in the auricular rate following the use of adrenalin in dogs with their vagi intact.

In a dog with a crushed auriculoventricular bundle, Routier<sup>5</sup> injected intravenously, 1/20 mg. of adrenalin and within twenty seconds observed an increase in both the auricular and the ventricular rates. Twenty seconds later there was a disappearance of the complete heart-block which lasted for twenty-five seconds. Routier was able to reproduce this experiment three times on the same animal and suggested the use of the

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drug in human heart-block because of its possible value in establishing normal rhythm and not because of its effect on the ventricular rate.

In a similar experiment Hardoy and Houssay<sup>6</sup> failed to establish normal rhythm in a dog with complete auriculoventricular dissociation with 0.2 c.c. (1/5 mg.) of a 1:1000 solution of adrenalin. They noted, however, an acceleration of both the auricular and ventricular rates as well as the appearance of premature ventricular beats.

#### REVIEW OF THE CLINICAL OBSERVATIONS

The first observations on the effects of adrenalin on patients with complete heart-block are those reported by Danielopolu and Danulescu.<sup>7</sup> In a man fifty-seven years of age with auriculoventricular dissociation and recurrent syncopal seizures, whose ventricular rate varied from 26 to 40 beats per minute, the injection of 1 mg. of adrenalin resulted within three or four minutes in an increase of both the auricular and the ventricular rates as well as the onset of premature ventricular beats. In a subsequent communication the same authors claimed to have been able to abolish a partial heart-block by means of this drug.<sup>8</sup>

Hardoy and Houssay<sup>6</sup> observed a similar acceleration of both the auricular and the ventricular rates one minute after the intravenous injection of 1 c.c. (1 mg.) of a 1:1000 solution of adrenalin in a man fifty-five years of age, with auriculoventricular dissociation and a regular ventricular rate of 30 to 32 beats per minute. Five minutes later there was a return to normal of both the auricular and the ventricular beats, but the P-waves of the electrocardiograms were at times negative. They quote Arrilaga<sup>9</sup> who observed the same phenomenon in several cases with auriculoventricular dissociation. None of these authors mention that their patients were subject to Stokes-Adams seizures.

Lutembacher's observations<sup>10</sup> with polygraphic tracings are of greater interest. He injected 0.5 mg. of adrenalin in a patient with auriculoventricular dissociation and a basic rate of 25 to 30 beats per minutes, and produced violent constriction of the chest which was followed by a "ventricular pause with syncope." The face became pale and this was followed by intense cyanosis with distention of the veins; then, after a short period of unconsciousness, there was a sudden increase in the ventricular rate to 84 beats per minute, which became regular when the patient regained consciousness. Seven minutes after, the heart beat at the rate of 40, but the patient still complained of severe precordial constriction. Twenty minutes later, the rate was still 40 and there was mental confusion, but on the following morning the patient's sensorium was clear and the pulse was 18. A second intravenous injection to this patient of 0.25 mg. of the drug, when the basic auricular and ventricular rates were 75 and 28, respectively, resulted in an immediate acceleration of the auricles to 85 beats and the ventricles to 75.

In another similar case the intravenous use of 0.1 mg. of the drug was followed by premature beats of the ventricles, tachysystole and finally cessation of "ventricular activity." Ten minutes after the injection both the auricular and the ventricular rates returned to normal. For eight days following this experiment the ventricular rate averaged 16 beats per minute.

In 1920 Strissower<sup>11</sup> injected adrenalin in a patient with complete auriculoventricular dissociation and noted an increase in the ventricular rate with a temporary return to normal rhythm. One month later, when the patient showed a partial heart-block with a two-to-one rhythm, the drug abolished the block, but only for a few seconds.

Two years later, Phear and Parkinson<sup>12</sup> studied a woman of forty-nine years with complete heart-block and frequently recurring syncopal seizures, in whom the subcutaneous injection of adrenalin was followed by complete cessation of the attacks within fifteen minutes. They suggested an extended trial of adrenalin in patients with Stokes-Adams seizures when the immediate loss of consciousness is normally due to extreme slowing and standstill of the ventricles, for these may be abolished by the increase in the ventricular rate due to the drug.

A somewhat similar case was reported by Feil<sup>13</sup> who noted cessation of syncopal attacks in a man fifty-six years of age with complete auriculoventricular dissociation, following the administration of 0.4 mg. of adrenalin. The attacks recurred twelve hours later and again twenty-four hours afterward, and on each occasion they were stopped by a similar injection.

In a man, aged forty-four years, with a rapidly increasing heart-block which became complete after thirty hours, Parkinson and Bain<sup>14</sup> used adrenalin on twelve separate occasions following the onset of Stokes-Adams seizures, and each time the drug abolished the attacks within three minutes. Freedom from attacks was maintained from two to forty-eight hours from the time of injection. On four occasions when partial block was present there was an increase of both the auricular and the ventricular rates with restoration of normal rhythm. At one time there was no increase in the ventricular rate with the use of the drug when the block was complete, while at another time there was definite increase.

In a woman, fifty-six years of age, Korns and Christie<sup>15</sup> injected intramuscularly 0.7 mg. of epinephrin and produced an increase in the auricular and ventricular rates, a marked auricular arrhythmia and many premature ventricular beats as well as an increase in the auriculoventricular block when the block was partial.

In summarizing the clinical results to date, the evidence shows that adrenalin in doses of from 0.3 mg. to 1 mg. when administered subcutaneously, intramuscularly or intravenously may accelerate both the auricular and the ventricular rates of patients with auriculoventricular

dissociation whether they are subject to Stokes-Adams seizures or not. The increase in rates may be regular or irregular. When the vagal effects of the drug predominate, the auricles may be slowed at first, and in patients with partial heart-block the block may be augmented. In a few instances normal rhythm could be established. In a small group of patients in whom syncopal seizures were found to be due to standstill of the ventricles, the drug was found to cause a cessation of the attacks, with or without an increase in the rate of the ventricles. In several instances, however, the use of the drug was followed by "syncope" with what appeared to be stoppage of the ventricles. For this unusual response no explanation has as yet been offered.

#### METHOD OF PROCEDURE

A 1:1000 solution of adrenalin was administered subcutaneously and intramuscularly in graded doses ranging from 0.3 mg. to 1 mg. to four patients with complete auriculoventricular dissociation suffering from transient syncopal seizures. In one patient an intracardiac injection was performed.

There were two males and two females. The heart-block in these patients was due, in all probability, to disease of the conduction system following coronary vessel closure. In the male patients it was definitely established that the syncopal attacks were the result of a marked slowing of the ventricular rate, whereas in the female patients the mechanism responsible for the attacks was found to be due to the various grades of ventricular acceleration leading to ventricular fibrillation.<sup>2, 10</sup> All of these tests were carried out at a time when the patients were known to be free from seizures for several days and when both basic auricular and ventricular rates were fairly constant and did not vary more than an average of 8 beats per minute.

In two instances also the drug was given during a syncopal seizure. The adrenalin was administered to the patients while they were in the electrocardiographic circuit, and records were taken as frequently as was thought necessary. During this time detailed notes were made of the patient's general reaction to the drug as well as of the clinical rate and rhythm of the pulse. Observations were discontinued in each instance four hours following the injections. Tests were not repeated on the same patient in less than two days.

#### RESULTS OBTAINED IN PATIENTS WITH COMPLETE AURICULOVENTRICULAR DISSOCIATION AND SYNCOPAL ATTACKS DUE TO VENTRICULAR STANDSTILL

In the two male patients in whom the syncopal seizures were due to a marked slowing of the ventricular rate, the intramuscular administration of 0.3 mg. of the drug resulted within three to five minutes in a progressive increase of the basic auricular and ventricular rates from an average of 78 and 34 beats per minute to 114 and 48 respectively. Ten minutes later the pulse rate was noted to be slightly irregular, and this was found to be due to an irregular spacing of the idioventricular beats and not to premature beats of the ventricles. The greatest increases in these rates were observed to come on from eight to ten minutes later. The patients at no time complained of any systemic symptoms, such as marked tremor, sweating, nervousness or palpitation of

the heart. The heart rates returned to their normal basic level within one-half hour after the injections.

The use of 1 mg. of adrenalin on a different occasion resulted in similar changes. Within one minute, the progressive accelerations in the rate described above began to appear, and these lasted a little over one hour and again there were no accompanying general disturbances.

In one patient, at a time when there was a slowing of the ventricular rate to 6 beats per minute with syncope which lasted for three minutes, the injection of 1 mg. of the drug intramuscularly, resulted within two minutes in a progressive acceleration of the ventricles. Ten minutes later these averaged 80 beats per minute and were regular. One hour later the ventricles returned to their normal basic rate of 24 beats after passing through a variable stage of irregularity consisting of an unequal spacing of the ventricular beats which, however, were all felt to come through at the pulse.

Premature ventricular beats were not recorded in them at any time during the use of adrenalin.

#### RESULTS OBTAINED IN PATIENTS WITH COMPLETE AURICULOVENTRICULAR DISSOCIATION AND SYNCOPAL ATTACKS DUE TO VENTRICULAR FIBRILLATION

The sequence of events following the use of adrenalin in the two patients in whom syncopal seizures were due to ventricular fibrillation was very variable.

The subcutaneous administration of 0.3 mg. of the drug resulted within three minutes, at one time, in an acceleration of the basic ventricular rate from an average of 38 beats per minute to 46. The auricular rates were barely influenced. Similar results followed the intramuscular injection with the same quantity of the drug, but the increase in the ventricular rate appeared after one minute and lasted fifteen minutes.

On another occasion the subcutaneous administration of 0.5 mg. of adrenalin was followed in one patient by an unusual sequence of events which deserves a detailed description.

Before the injection the basic ventricular rate was regular and averaged 26 to 28 beats per minute. The auricular rate was 73 beats per minute (Fig. 1 A). The auricular complexes of the electrocardiogram were upright and alike from beat to beat. The ventricular complexes were also upright but varied occasionally in size, shape and form.

One and a half minutes after the injection, the pulse at the wrist began to show coupling which persisted for twenty seconds and then there was a sudden pause. On listening over the apical region four distinct but progressively weaker heart sounds could be heard preceding this pause. At the same time the patient's eyes closed, she lost consciousness, the face assumed a deathly pallor which was followed by

intense cyanosis, and this changed suddenly to a bright red flush of the face which coincided with a heart beat coming through at the pulse. This whole period lasted only fourteen seconds, following which the pulse became regular again for about another one and one-half minutes.

The electrocardiograms recorded during the period of clinical bigeminy (Fig. 2), showed the auricular rate to be 75 beats per minute and regular and the complexes all of the upright form. The complexes of the basic ventricular rhythm were of high voltage (Fig. 2 *A, B*) as compared with those prior to the use of the drug and, the T-waves were of unusual shape and form, becoming progressively larger in size from beat to beat (Fig. 2 *C, D, E*).

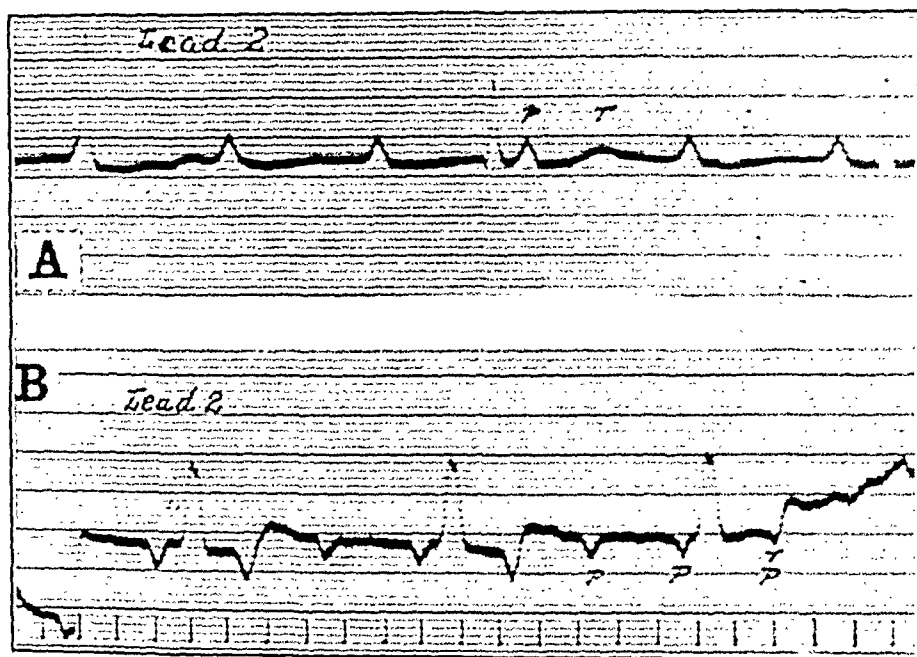


Fig. 1.—(The time in all of these records is in fifths of a second.) *A*, Before the injection of adrenalin, the auricular rate was 73 and the ventricular rate was 26. The auricular complexes are all positive. *B*, Fifteen minutes later the auricular rate was 125 and the ventricular rate was 41. Both the T- and P-waves were markedly negative.

During the absence of the pulse, the electrocardiograms showed ventricular oscillations of a variable voltage from beat to beat (1 to 20 mm. high) irregular in their time relationship to each other (Fig. 2 *F, G*) with a duration of from 0.04 to 0.28 seconds each.

The auricular beats were not visible at this time. They reappeared irregularly as consciousness was restored when the ventricles assumed an almost regular rhythm and rate independent of their relation to the auricles (Fig. 2 *H, L*). The ventricular complexes were all slightly notched indicating probably that they arose from a different focus from that of the basic complexes.

Three minutes after these events, the patient began to sigh heavily. On examining her pulse it was found to be more rapid than previously and at times coupled; frequently three and four successive but weaker

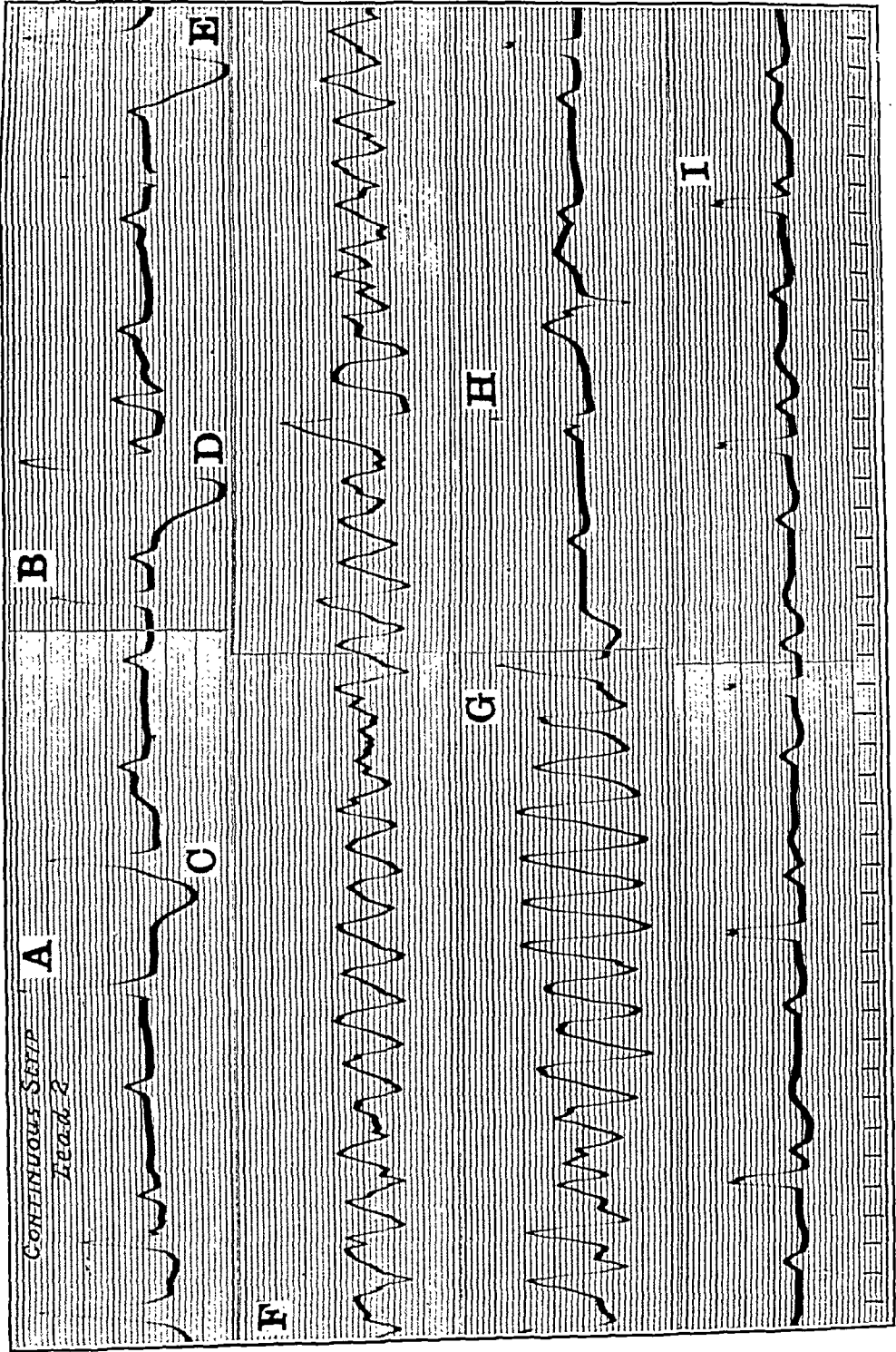


Fig. 2.—One and a half minutes after the injection of adrenalin. The basic ventricular complexes are large (A, B). The T-waves are now markedly negative and extremely large (C, D, E). There is bigeminal rhythm before a short period of ventricular fibrillation sets in (F, G).

beats could be felt, only the first two, however, being audible at the apex of the heart. The rate increased progressively and the electrocardiograms indicate this to be due to a recurrent grouping of ventricular oscillations following rapidly the basic ventricular complexes (Fig. 3 *A, B, C*) with an auricular rate which now averaged 140 beats per minute (Fig. 3).

After two minutes of this type of rhythm there again occurred an absence of the radial pulse which now lasted one minute and four seconds (Fig. 4).

The clinical syndrome this time resembled the characteristic Stokes-Adams seizures from which this patient suffered and which have been adequately described in another communication.<sup>16</sup>

The electrocardiograms again revealed a series of oscillations characteristic of ventricular fibrillation ending in spontaneous revival. Recovery of the basic rate was preceded by an idioventricular rhythm with retrograde auricular beats, most of which were superimposed upon the T-waves of the preceding ventricular complexes.

The ventricular rate, however, gradually increased to 41 beats per minute and the auricular rate to 125 before a period of ventricular tachysystole appeared fifteen minutes after the injection of adrenalin.

At this time the auricular complexes were at first negative (Fig. 1 *B*) but later they became positive as the ventricles assumed an irregular rate of 60 to 115 beats per minute, with impulses which appeared to be rising from various foci in the ventricles, although most of them were downward in character as compared with the complexes of the basic rhythm (Fig. 5).

Twenty minutes after the injection the ventricular rate returned to a level of 42 beats per minute (Fig. 6), and the auricles were beating at 125 beats before they suddenly began to fibrillate. The auricular fibrillation persisted for almost two hours following the use of adrenalin.

For the ensuing three hours there were no more recurrences of these irregularities described although the patient complained of persistent constriction of the chest for the rest of the day.

Subsequent observations revealed that short periods of ventricular fibrillation could be induced in her with 0.5 mg. of the drug given intramuscularly even in the presence of partial heart-block with a two-to-one rhythm.

However, at such times, the partial heart-block would be increased at first before there followed a gradual acceleration of both the auricular and ventricular rates leading eventually to the development of premature beats of the ventricles. These at first occurred singly, then in groups and ended finally in ventricular fibrillation. The longest period of ventricular fibrillation with syncope recorded in this patient as a result of adrenalin administration was one minute and four seconds, followed by spontaneous recovery.



Fig. 3.—Three minutes after the injection of adrenalin. Recurrent groupings of aberrant ventricular oscillations (A, B, D). The auricular rate is now 140 beats per minute.



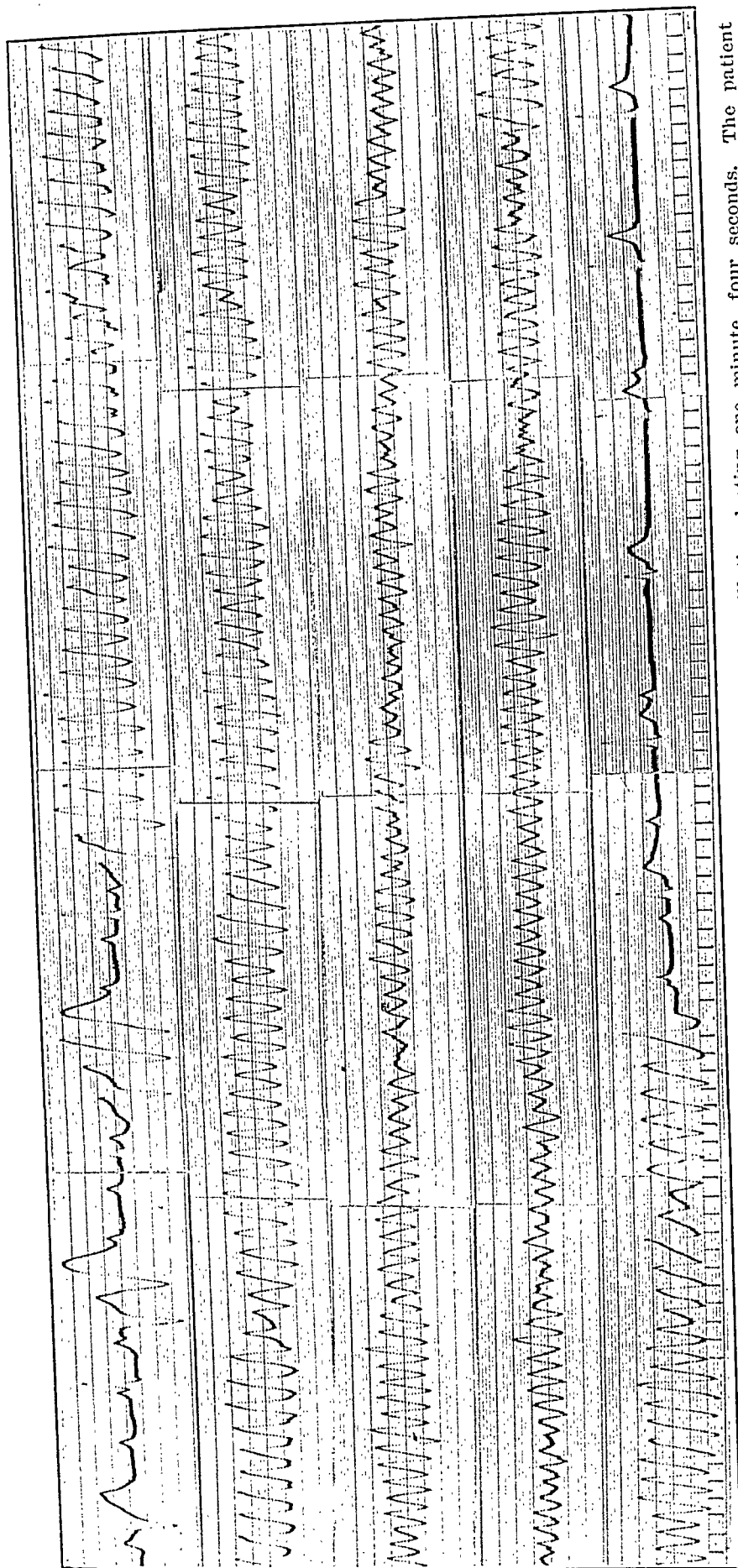


Fig. 4.—Five minutes after the injection of adrenalin. A transient period of ventricular fibrillation lasting one minute, four seconds. The patient was in syncope during this entire period.

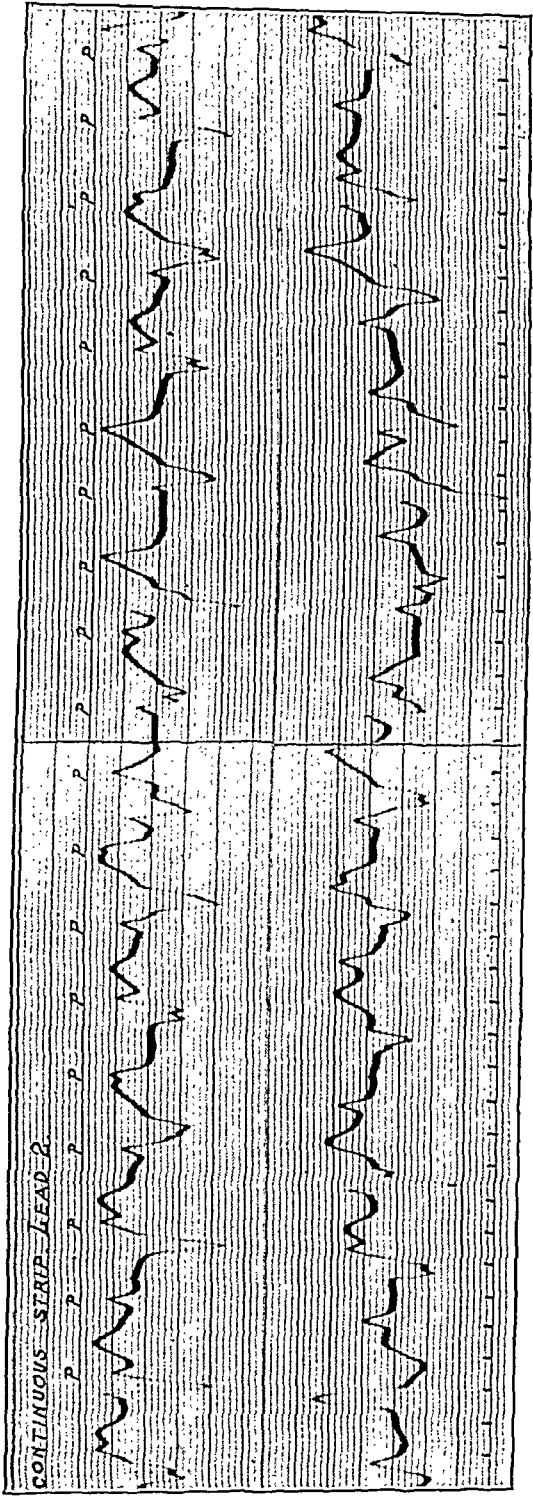


Fig. 5.—Fifteen minutes after the injection of adrenalin. This record was obtained thirty seconds after that in Fig. 1 B. The auricular rate is 115 and the auricular complexes are positive. The ventricular rate varies between 60 and 115 beats per minute.

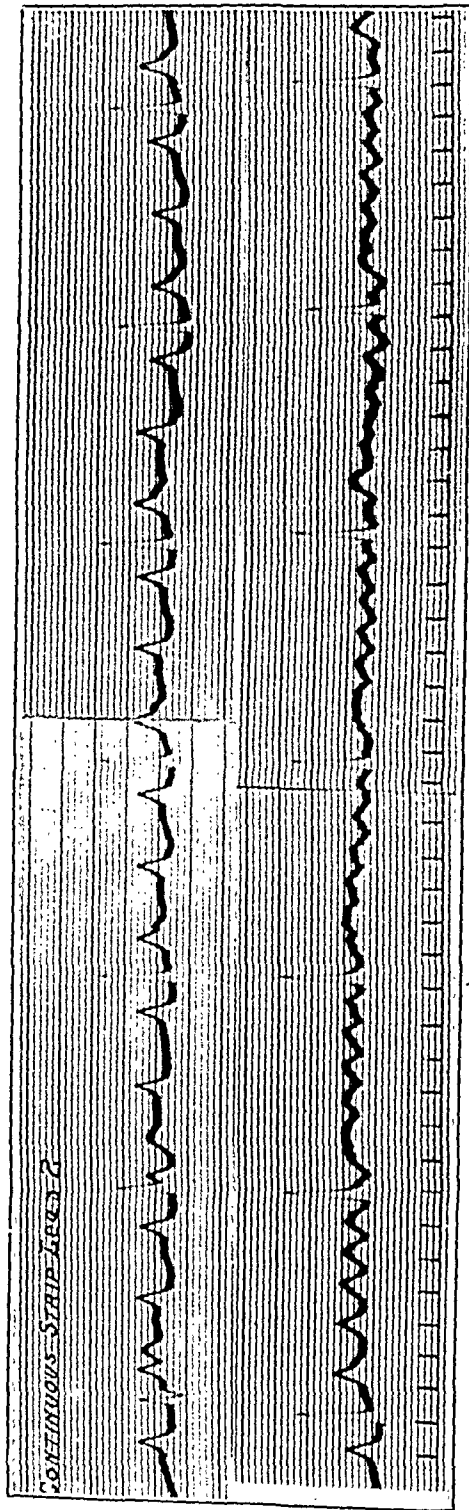


Fig. 6.—Twenty minutes after the injection of adrenalin. Transient auricular fibrillation, which persisted for two hours.

In the second patient, in whom ventricular fibrillation was the mechanism responsible for syncopal seizures, the intramuscular administration of 0.5 mg. of the drug resulted in a series of events similar to those described above but in a more severe form. Short periods of syncope due to ventricular fibrillation varying in duration from fifty seconds to one minute and fourteen seconds, alternated with periods of regular rhythm with a ventricular rate which averaged from 60 to 115 beats per minute. This sequence of events lasted for almost one hour before restoration of the basic rhythm took place. For the ensuing two hours there were recorded many premature beats of the ventricles, all of which, however, came through at the pulse.

On another occasion, the subcutaneous administration of a similar dose resulted only in an increase of the basic ventricular rate to a few beats per minute above the normal.

Finally, at a time when the patient had been in syncope for seven minutes and her respirations had ceased following a seizure of ventricular fibrillation, 1 mg. of adrenalin was injected directly into the heart. About one minute later, a strong beat at the pulse was seen to coincide with a flush of the face. Respirations were not re-established, however. For the next minute the ventricular rate increased to 115 beats per minute only to be followed again by a short run of ventricular fibrillation. Within the next thirteen minutes the heart rhythm, in the presence of loss of consciousness and absent respirations, consisted of a series of rapidly recurring periods of ventricular fibrillation alternating with a tachysystole of the ventricles, the end of which, however, could not be recorded graphically. Auricular fibrillation was never registered in this case.

#### DISCUSSION

The rational use of adrenalin in patients with auriculoventricular dissociation subject to Stokes-Adams seizures, depends upon an intimate knowledge of the mechanism responsible for the syncopal attacks.

It is important to appreciate that where a reduction in the ventricular rate or ventricular standstill is the cause of cerebral anemia resulting in syncope, adrenalin is the drug of choice. In such instances it may be used effectively in doses of 0.5 mg. to 1 mg. given intramuscularly. Judging from the electrocardiograms, it produces its effects on the rate and rhythm of the heart within one to three minutes following the injection. The results obtained are an increase in the idioventricular rate primarily through a stimulation of the idioventricular pacemaker. This increase is sometimes regular and at other times irregular. It reaches its maximum beneficial effects rapidly and lasts as long as four and one-half hours, when the rate slows down, at times to a level lower than that of the basic rhythm.

Even when the ventricular rate has already reached its basic level.

the repeated injections of adrenalin may prevent a slowing of the ventricular rate with resulting syncope. In patients with auriculoventricular dissociation the drug does this by maintaining a threshold of enhanced irritability of the auriculoventricular node. Excellent results have also been reported in such cases in which syncopal seizures have been prevented by the combined use of barium chloride<sup>17</sup> with adrenalin.<sup>18</sup> In cases refractory to adrenalin alone, the former drug increases the irritability of the idioventricular pacemaker and makes it more susceptible to the influence of adrenalin.

In patients with Stokes-Adams seizures due to ventricular fibrillation, however, the ventricles as well as the idioventricular pacemaker are already in a state of enhanced irritability. Therefore adrenalin is contraindicated both during the period of syncope and during the intervals between attacks. Our experience does not support the suggestion made by Dock<sup>19</sup> that small doses of the drug may cause ventricular fibrillation and large doses may arrest it.

It is possible that the small doses used by Lutembacher<sup>10</sup> where he observed "stoppage" of the heart and recorded a straight line in his polygraphic tracings also produced ventricular fibrillation, for both standstill of the ventricles and ventricular fibrillation give the same polygraphic records of the pulse during syncope, namely, a straight line indicating absent effectual contractions of the heart.

It should be apparent from these studies that the response to adrenalin as judged by the changes in the heart rhythm and rates of these patients is very variable from time to time. This variation is due neither to the drug nor to its mode of administration but probably to the state of irritability of the neuromuscular tissue of the heart. We have repeatedly observed marked systemic reactions, such as violent tremors, profuse diaphoresis and high rises in blood pressure, in the absence of any effects of the drug upon the cardiac rhythm.

Mention should be made here that our experience with the intramuscular injection of adrenalin in such patients has been limited to cases where the slowest ventricular rate during a period of syncope has been 6 beats per minute. It is obvious that absorption can take place in these cases as soon as the circulation is established, even by one effectual ventricular beat. It has been suggested that where complete standstill of the ventricles is responsible for syncope, adrenalin should be used intracardially, as has been done successfully by Levine and Matton<sup>20</sup> in one of their patients in whom standstill of the ventricles was recorded following a long period of ventricular fibrillation. However, in view of the fact that we have observed the effects of adrenalin on the heart during a period of ventricular fibrillation to be the same intramuscularly as it was intracardially, it is probable that the drug influences the heart rhythm and rate in another manner than through the circulating

blood stream, possibly through the sympathetic nervous system. Much more work will have to be carried out on this phase of adrenalin absorption before we may be certain of how it reaches the heart from the periphery when the circulation is at a standstill.

It may be questioned whether the electrocardiograms obtained in the two patients with syncopal seizures due to ventricular fibrillation following adrenalin were due to the drug, rather than to the natural course of events in such patients. For the records obtained during syncope following adrenalin resemble in every respect those obtained when syncope occurred spontaneously.<sup>2</sup> The progressive increase in the auricular rate during the premonitory period after adrenalin administration, the marked negativity of the P-waves following the fibrillatory period, the unusual tachysystole recorded before the restoration of the basic rhythm as well as the development of transient auricular fibrillation, all support the contention that the drug was responsible for these events. None of these phenomena was noted to have come spontaneously in this sequence, in a study of over one hundred recorded seizures of transient ventricular fibrillation in this patient.

#### SUMMARY AND CONCLUSIONS

Four patients who had complete auriculoventricular dissociation and who were subject to syncopal seizures received adrenalin in varying dosages. In two of the patients the syncopal attacks were due to a slowing of the ventricular rate, while in the other two the syncopal seizures were associated with transient periods of ventricular fibrillation.

The same dose of adrenalin was found to act variably at different times in the same patient when administered either subcutaneously or intramuscularly.

Adrenalin was found to increase both the auricular and the ventricular rates of the patients in whom the syncopal seizures were due to standstill of the ventricles. The increases in these rates were observed both preceding and during the Stokes-Adams attacks and were both regular and irregular in rhythm. The drug produced its effects primarily through a direct stimulation of the idioventricular pacemaker.

Adrenalin induced short periods of transient ventricular fibrillation with syncope in two patients in whom the Stokes-Adams attacks were found to be due to ventricular fibrillation. In one of these patients the drug also produced auricular fibrillation and a tachysystole of the ventricles which lasted on and off for several hours at one time.

In one patient with already established ventricular fibrillation the intracardiac injection of 1 mg. of the drug seemed to perpetuate the mechanism resulting in alternating periods of ventricular fibrillation with tachysystole lasting over thirteen minutes and ending in death.

As a therapeutic measure adrenalin is a life saving drug in patients in whom syncopal seizures are due to a slowing of the ventricular rate.

It is distinctly contraindicated in those in whom the attacks are the result of ventricular fibrillation, and its indiscriminate administration in such patients may result in death.

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AURICULOVENTRICULAR NODAL PAROXYSMAL TACHY-  
CARDIA AND AURICULAR FLUTTER.  
CASE REPORT\*

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THE purpose of this paper is to present a very unusual example of cardiac arrhythmia observed in a patient admitted to the Worcester City Hospital because of an acute bronchopneumonia. The electrocardiographic diagnosis was auriculoventricular nodal paroxysmal tachycardia, interrupted at varying intervals by auricular flutter with varying degrees of heart-block. A-V nodal paroxysmal tachycardia is of itself a rather rare form of arrhythmia, having occurred only four times in a series of 10,000 patients (0.04 per cent) whose electrocardiograms were recorded at the Massachusetts General Hospital over a period of sixteen years (1914-1930).<sup>1</sup> At the Mayo Clinic over a period of nine years (1914-1923), 102 cases of paroxysmal tachycardia were electrocardiographed. Only three of these had an R-P interval as demonstrated in the case to be discussed.<sup>2</sup> However, the case which we are presenting has its claim to distinction in the fact that the nodal rhythm is interrupted by short runs of flutter, with varying block. No exactly parallel case has been observed in a careful search of the literature. P. D. White describes the course of a patient who had auricular flutter which digitalis converted to auricular fibrillation and then to a rhythm which had its origin in the A-V junctional tissues.<sup>3</sup> W. E. Hume, by means of the polygraph, was able to demonstrate, in two cases of diphtheria, the transition of an A-V nodal rhythm (not paroxysmal tachycardia) into auricular flutter, terminating in death for the patients.<sup>4</sup> Two cases which to some extent approach the case at hand have been reported by Géraudel. These patients were observed over a period of from two to four years. Tracings at certain periods showed rhythm simulating either a nodal tachycardia or an auricular tachycardia. At other times flutter with 2-1 block was found and occasionally a third phase was recorded in which there would be groups of two, three, and four ventricular complexes similar to those found in the period of tachycardia—each with its own auricular or nodal origin. Then would come two auricular contractions to one of the ventricular contractions (flutter with 2-1 block) seemingly linking up the two phases. In view of these findings the author drew the conclusions that paroxysmal tachycardia did not exist at all but was simulated by a flutter with a 1-1 response.<sup>5</sup> There can be no question of the distinction of the two rhythms in the case at hand (i.e., A-V nodal paroxysmal tachycardia and auricular flutter).

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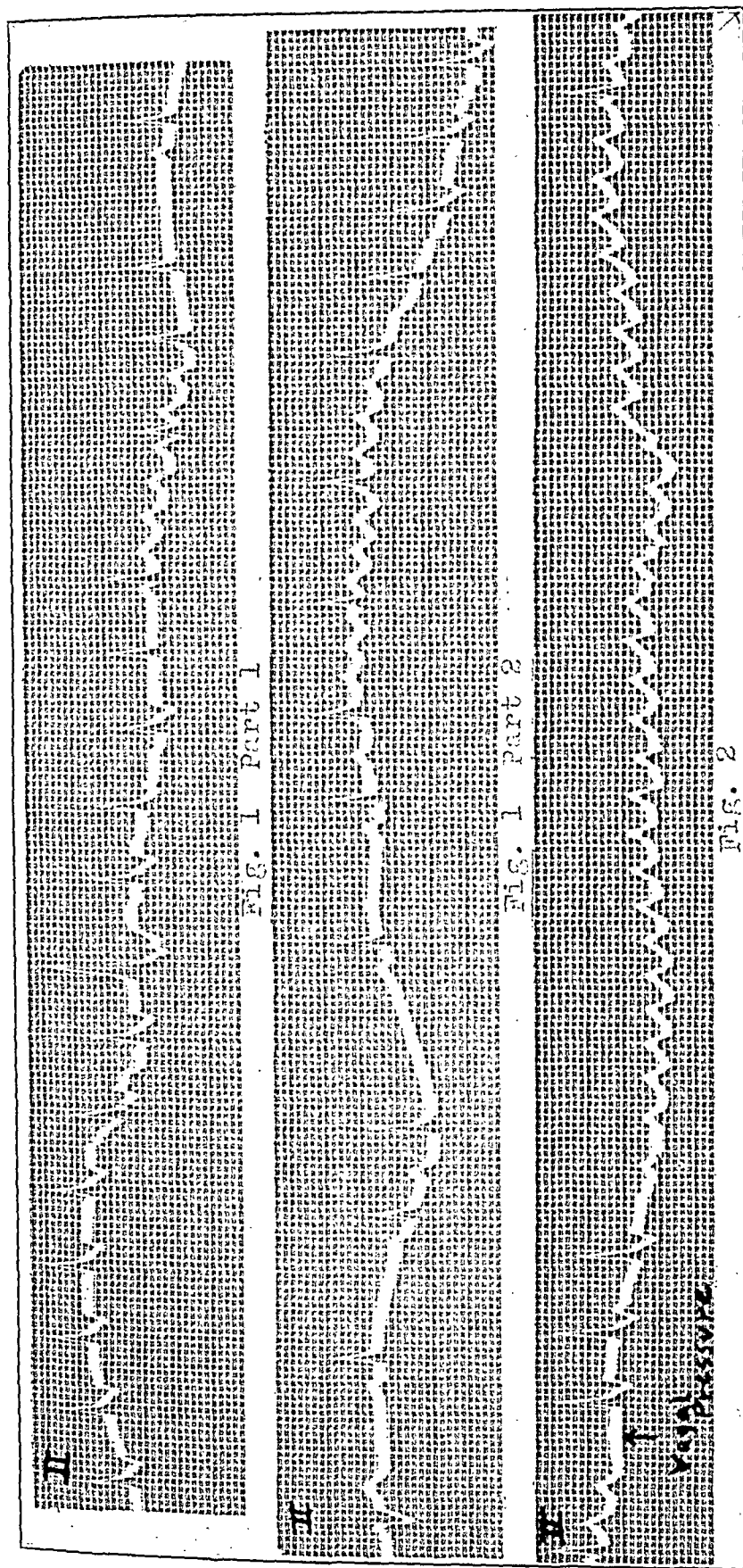


Fig. 1.—Electrocardiogram (Lead II) showing A-V nodal tachycardia interrupted by short periods of auricular flutter and by auricular and ventricular premature beats (see text). Part 2 is a continuation of Part 1.

Fig. 2.—Effect of vagal pressure, applied at the end of a period of auricular flutter and during a short run of beats of A-V nodal tachycardia, showing 29-1 heart-block in a succeeding interval of auricular flutter.

## CASE REPORT

*History.*—The patient, a forty-three-year-old married man, entered the Hospital on September 15, 1931, having been sick five days at home. He complained chiefly of pain in the left upper chest. Five days previously he was playing with his dog when he was seized with a sharp pain over the tops of both shoulders. There

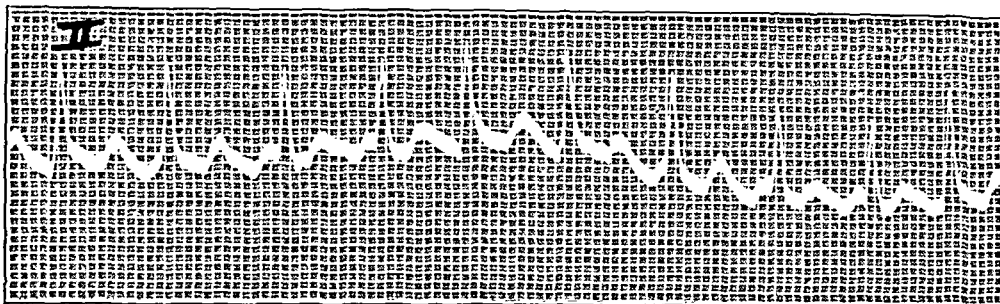


Fig. 3.—Electrocardiogram after quinidine sulphate showing auricular flutter with two-to-one block.

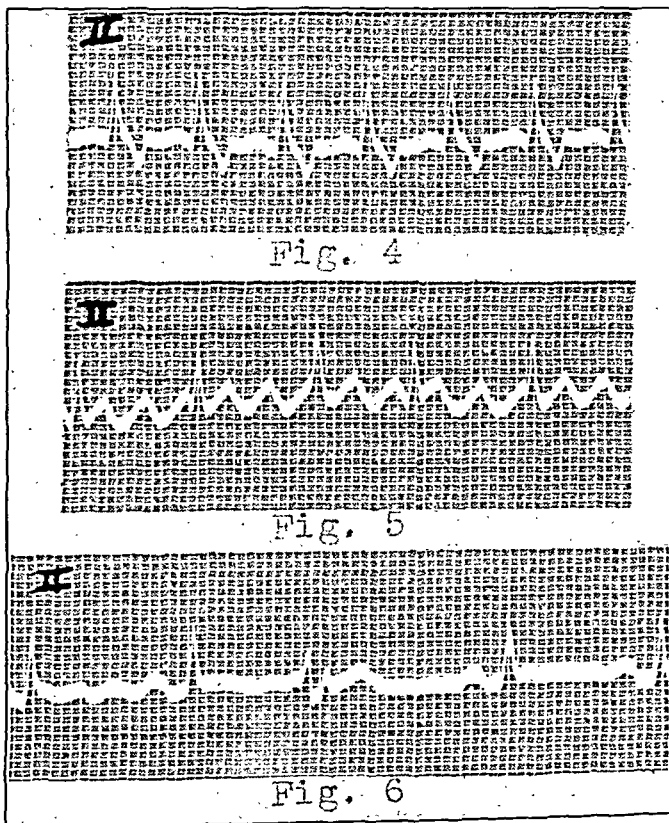


Fig. 4.—A-V nodal paroxysmal tachycardia before atropine sulphate.

Fig. 5.—Auricular flutter with two-to-one and three-to-one block, one minute after atropine sulphate.

Fig. 6.—Return to normal rhythm, four minutes after atropine sulphate.

were no chills, cough, or pain on respiration. This pain lasted three to four days and was not severe enough to make him go to bed. The following day he felt a tightness in the left axillary line at the level of his heart and had some difficulty in breathing. Two days before admission to the hospital he commenced to cough a bit and felt feverish.

*Family History.*—Irrelevant.

*Past History.*—He had rheumatic fever at fifteen years of age, at which time he was laid up for one year. Since then he has never had dyspnea, edema, precordial pain or distress, or any symptoms suggestive of cardiac failure. He has, however, as long as he can remember, been conscious of marked variations in his pulse rate. Particularly after exercise, such as golf, is he conscious of a very rapid pounding of his heart. This palpitation may suddenly stop of its own accord; at other times he is able to terminate the attack by holding his breath or by bending forward. Aside from this abnormality the patient has always been well.

*Physical Examination.*—A middle-aged man with flushed face sitting up in bed breathing rapidly. His temperature was  $101^{\circ}$ , pulse 134 and regular, respirations 40. Examination of the lungs showed dullness to percussion at both bases with coarse râles extending up to the angles of the scapulae. These signs were more extensive on the left than on the right. No points of consolidation were made out. The heart was thought to be enlarged to percussion. The sounds were of good quality.

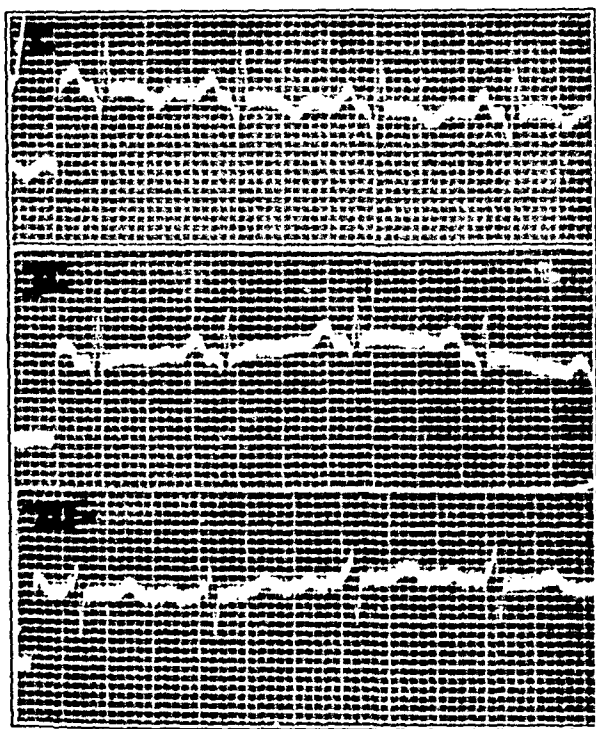


Fig. 7.—Showing patient's normal rhythm at the follow-up visit.

No murmurs were heard. The blood pressure was 140 mm. systolic and 100 diastolic. Physical examination was otherwise not abnormal.

*Laboratory Findings.*—The urine examinations were normal. The white blood cell count was 18,000. The sputum contained group IV Pneumococcus. The basal metabolism was not elevated. The Wassermann reaction was not recorded.

*Progress.*—The temperature and respirations gradually fell to normal over a period of six days. For the next few days the patient's pulse rate was quite variable. Sometimes it would be 130 to 140; at other times it would be 70; sometimes it would be irregular; other times regular. The patient insisted if he were allowed to get up his heart would return to its normal condition. Consequently on the seventh day following the drop in temperature he was allowed up. As he had predicted, his pulse became quite regular with only occasional paroxysms of tachycardia. Although the diagnosis in this case was acute bronchopneumonia the patient was given digitalis perhaps rather empirically. With the fall in temperature on the sixth day digitalis was omitted. He had received  $19\frac{1}{2}$  grains.

There had been no other medication of note. He was discharged on the fourteenth day.

The patient came to the hospital November 23, 1931 (eight weeks after his discharge) for a follow-up visit. He stated that he was feeling very well indeed. At night he might have an occasional attack of palpitation just after getting into bed. The attack would last only a few minutes and seemed never to occur during the daytime. Examination of the heart revealed no further abnormalities than found at the previous examination. An electrocardiogram was taken, the three leads of which are to be seen in Fig. 7.

#### ELECTROCARDIOGRAPHIC OBSERVATIONS

Our observations on the patient's cardiac abnormalities were made from the time his temperature fell to normal on the sixth day. The first electrocardiogram was taken on the sixth day. (Fig. 1. Part 2 is a continuation of Part 1.\*) The initial rhythm is a tachycardia (rate 160) with an impulse arising at or near the A-V node (i.e., an A-V nodal tachycardia). The wave of origin of the impulse is incorporated in the QRS complex and there is a retrogression of the impulse into the auricle to produce an inverted P-wave directly following the QRS, thus producing an R-P interval. This type of tachycardia is interrupted at one point by a paroxysm of auricular flutter first with a 4-1 block and then a 3-1 block. The next complex is an escaped ventricular beat. Following this is a contraction whose origin is supraventricular, though not at the usual site in the S-A node. (Compare normal rhythm in Fig. 7.) Next there appears a premature ventricular beat following which the heart returns to its normal S-A rhythm, but for two contractions only. A premature auricular beat intercedes, coming from an ectopic focus. Shortly later there appears another paroxysm of auricular flutter which seems to be initiated by a premature auricular beat. First there is a 3-1 block and then 4-1 and 3-1 block. Finally the heart reverts to a typical A-V nodal paroxysmal tachycardia.

*Effect of Vagal Pressure.*—Pressure on the right carotid sheath was applied at a time when the heart was responding to the nodal focus (Fig. 2). A condition of ventricular standstill was produced which lasted for a period of 6.2 seconds. During this period there was an isolated P-wave followed by a regular action of the auricle at a rate of about 300 per minute. This situation did not bother the patient subjectively. He stated that he felt dizzy. He did not lose consciousness. This was the only time that we were able to produce such a vagal effect.

*Effect of Quinidine Sulphate.*—After taking the above electrocardiograms, twelve grains of quinidine sulphate were given, with no change in the rhythm. Fifteen grains were given on each of the next two days. On the third day the rate was found to be 150 and apparently regular. The patient was then given twenty-one grains of quinidine, at which point he complained of ringing in the ears. He was conscious

\*Lead II is used in the figures except where otherwise indicated.

(more so than usual) of his heart's beating and complained that he had felt worse since the quinidine treatment had been instituted. A tracing was then taken (Fig. 3) showing a slight irregularity of incidence of the ventricular contractions at a rate of 150 to the minute. A flutter with a 2-1 block is the dominant rhythm and no instance of the A-V nodal rhythm was found. Deep breathing did not affect this tracing. Vagal pressure served temporarily to increase the block to 4-1 and then to 3-1. We were unable to obtain a normal sinus rhythm after moderate doses of quinidine sulphate.

*Effect of Atropine Sulphate.*—On the following day the electrocardiogram showed a return to A-V nodal paroxysmal tachycardia (Fig. 4). Atropine sulphate 1/100 grain was injected subcutaneously. In one minute there was a flutter with block changing from 2-1 to 3-1 (Fig. 5). This persisted for three more minutes when the heart returned to a normal sinus rhythm (Fig. 6) with an occasional premature nodal beat at a rate of 100. After six minutes the normal rhythm was displaced by a flutter with varying block. Forced expiration would sometimes convert the flutter to a normal rhythm.

Atropine was given, grains 1/100 by mouth, every four hours for forty-eight hours and then reduced to grains 1/150 every four hours and a tracing taken on the third day following. Considerable irregularity of the heart beat was still present. The cardiogram showed a tendency to coupling with a normal sinus beat followed by a premature auricular beat though at times the rhythm became normal or would change to the nodal tachycardia.

#### DISCUSSION

This patient evidently had a very irritable heart. The rôle of the pacemaker is at times usurped by a focus of rapid impulse formation at or near the A-V node. At other times this nodal focus is supplanted by a focus higher up in the auricle where there is a regular circus movement forming impulses twice as fast as the nodal focus (the interval between ventricular beats in the periods of tachycardia, representing the intervals between nodal impulses, is twice as long as the interval between P-waves in the stages of flutter). A flutter with 2-1 and increasing block then develops. Apparently there are two areas of abnormal impulse formation, the one in the A-V node causing a paroxysmal tachycardia, the other focus occurring higher up and instituting a state of flutter. First one area comes into control, then is gradually displaced by the other area. A very disordered heart beat results.

Vagal pressure may exert a greater effect in A-V rhythm than in S-A rhythm.<sup>6</sup> Vagal stimulation in this case produced a 29-1 block, the auricle contracting twenty-nine times in response to the upper

focus. The auricular rate is the same as at the periods of flutter scattered through the runs of nodal tachycardia.

The S-A node though greatly depressed has not lost its function as evidenced by the occasional instances of normal sinus rhythm. Atropine by its paralyzing action on the vagus nerve endings seems to remove this inhibition, allowing the S-A node to resume its normal rôle for short periods of time. However, its reign is apt to be terminated at any moment by the return of control by the ectopic foci.

#### SUMMARY

A case of peculiar cardiac arrhythmia is reported in a man forty-three years old, and electrocardiograms showing the mechanism of the disordered heart beat are presented. The dominant rhythm is an auriculoventricular nodal paroxysmal tachycardia which at varying intervals becomes displaced by an auricular flutter with changing block. The effects of vagal pressure, quinidine sulphate, and atropine sulphate on this disordered rhythm are demonstrated.

The author of this paper wishes to acknowledge the kind assistance of Dr. P. D. White of Boston in reporting this case, and the interest of Dr. G. M. Albee of Worcester whose patient it is who forms the subject matter for this report.

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# Department of Clinical Reports

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## ACUTE PULMONARY EDEMA

### REPORT OF A CASE WITH AUTOPSY\*

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THIS term was first used by Huchard<sup>1</sup> in 1897 to describe the case of a patient suffering from a cardiac condition complicated by sudden and severe attacks of edema of the lungs. Numerous writers since then have written of this condition under various captions as cardiac asthma, paroxysmal acute dyspnea and paroxysmal dyspnea of hypertension. Palmer and White<sup>2</sup> in an excellent summary described it as a "condition of paroxysmal acute dyspnea, generally occurring at night, but sometimes following exertion, lasting from minutes to hours and accompanied by a sense of suffocation, by wheezing and often by cough with frothy sputum which may or may not be bloody and which is due fundamentally to serious heart disease, especially involving the left ventricle, the attack being characteristically relieved by morphine."

Just as the terminology describing these attacks has differed, so has the exact nature of the attack and the causation been subject to various interpretations. The earliest and most outstanding experimental work was done by William Henry Welch<sup>3</sup> in 1878, in which he injured the left ventricle of rabbits producing a pulmonary edema. According to Welch, the condition is one in which "A disproportion exists between the working power of the left ventricle and of the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time, the same quantity of blood as the right heart." Cohnheim at once supported this theory but Sahli and Grossman criticized it though they offered no experimental evidence to refute it, nor any equally satisfactory explanation. Vaquez considers several possible causes, the mechanical, the angioneurotic, the toxic and the mixed forms. He favors apparently the idea that most of the attacks can be laid directly to failure of the left ventricle. Pratt,<sup>5</sup> in a review of thirty-nine cases of cardiac asthma, feels that a peripheral vasomotor disturbance is a strong factor in many cases, and also suggests that there may be an element of bronchial spasm present. The opinion of Palmer and White is that left ventricular strain and failure cause, with increased blood flow, a stasis of blood in the pulmonary circulation, the right ventricle sending too much blood for the left ventricle to take care of. Practically all writers agree that the one most important associated finding in all cases of acute pulmonary edema is a

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marked coronary sclerosis. This interferes with coronary flow, causes myocardial ischemia and failure on the part of the ventricle to maintain a required output.

This paper does not concern itself with the pulmonary edema of cardiac decompensation accompanying valvular disease, nor do we refer to the gradually developing edema seen in the failing heart of myocarditis either of the fibrous or infectious type. Edema of the lungs occurring in allergic cases, chronic infections, bronchitis and so-called angioneurotic conditions differs clinically and symptomatically from the acute or paroxysmal type. The condition is fundamentally the result of sudden left ventricular overstrain plus acute myocardial failure with all the concomitant symptoms of complete collapse. The ashen pallor, urgent dyspnea, cold surface, clammy sweat, rapid pulse, fall of tension and hopeless expression of the patient, create a singular picture seen in no other form of pulmonary edema. Recovery from the seizure is equally striking. The patient's sensation of relief from overpowering oppression, the cessation of sweating, the return of body warmth, are soon followed by a lessening of the tachycardia, a fuller pulse, a return of color and a gradual vanishing of the dyspnea and signs of pulmonary edema. The attack may be very mild, so slight that only the patient senses a feeling of difficult breathing and perhaps some alarm. If the seizure progresses it may develop with aggravating intensity and result in death in a few minutes. The entire episode may be over in a few minutes, or it may progress with alarming intensity, reach its climax, slowly subside and be completely over in an hour.

After repeated attacks, the period of recovery is prolonged. However, when all the features have vanished, no objective or physical signs remain or even suggest that the patient has passed through a critical seizure. Though this condition is not infrequent in practice, the opportunity for prolonged observation and for intensive clinical study of a case of acute pulmonary edema is not common.

In the report given below not only was the patient seen prior to his initial attack but in each subsequent seizure it was possible to make clinical and electrocardiographic studies, observe the factors that precipitated each attack and note the effects of various forms of medication. Supplementing the prolonged observation of this case, the autopsy findings revealed definite changes that supported the explanation of left ventricular myocardial damage.

#### CASE HISTORY

Male, aged sixty-two years, married, merchant, came for physical examination for the first time in 1916. He felt perfectly well but expressed the desire to have regular and complete examinations. Noteworthy in his family history were the facts that his mother, aunt and uncle had died of diabetes and that his father and brother had died of coronary disease. One sister was living and well. There was nothing of importance in his past or personal history. There was no history of rheumatism, and syphilis was denied. At the time of the initial examination,



a mild hypertension, 150 systolic and 90 diastolic, was recorded. There was no evidence of cardiac enlargement. On subsequent occasions during the next six years the blood pressure was recorded at various heights, the maximum ever found was 184 systolic and 110 diastolic. Several times traces of albumin and a rare hyaline cast were reported in the urine.

In 1922 the patient complained for the first time of pain in his chest radiating into the left arm, made worse by exertion and accompanied by fear of possible consequences. Whether the *angor animi* was spontaneous or due to the patient's knowledge of symptoms of the disease, could never be determined. During the next few years the increasing frequency and severity left no doubt of the fact that these were attacks of stenocardia on the basis of a coronary sclerosis. With this in mind general directions concerning restrictions in activity, mental strain, diet and habits together with instructions with regard to the use of nitroglycerine, were given. In 1925, he had his first paroxysm of acute pulmonary edema. It came on with exercise; it was relieved by one-fourth grain of morphine. Two years elapsed before he had a return of a similar condition though in the meantime he continued to have anginal attacks of varying intensity. He carried nitroglycerine constantly and used it liberally with benefit. In 1927 he began having attacks of pulmonary edema more frequently so that between that time and his death in October, 1930, he was seen in some attacks of great severity.

*Physical examination* revealed a small man weighing 65 kg. His skin was smooth and dry and his musculature was poorly developed. There was slight enlargement of the heart to the left and downward. The sounds were clear; the aortic second was moderately accentuated. There was normal vesicular breathing throughout the lungs. The edge of the liver could be felt on deep breathing. The abdomen was otherwise normal. Though his blood pressure maintained a higher level up to 1925, after that it gradually fell, averaging during the last five years 150 systolic and 100 diastolic. The blood count was normal. The Wassermann test was negative. X-ray films revealed a slight enlargement of the left ventricle. There was no change in appearance of the aortic shadow. The lung fields were clear. There was moderate hilus infiltration. The phrenocosto angles were clear. Electrocardiograms revealed changes indicating marked disease of the coronary arteries.

*Course of the Disease.*—Although the patient suffered almost daily attacks of stenocardia from 1927 up to his fatal seizure in 1930, he nevertheless remained active in business and continued with moderate exercise. He played golf in pleasant weather and spent much leisure time at cards. Neither moderate work nor recreation were harmful. Physical and emotional strain precipitated attacks. Overeating and excessive smoking had a similar effect. Yet the patient knew his limitations and managed to live within them. He took a philosophic view of his condition and tried to avoid those forms of excitement, overactivity, and indulgence that would precipitate stenocardia. However, he chose moderate freedom to excessive restraint, preferring to control the pain with nitroglycerine. This was accomplished effectively with 1/100 grain of nitroglycerine which the patient repeated sometimes at fifteen-minute intervals.

During the last three years of his life, attacks of acute pulmonary edema also became increasingly frequent. The attacks of edema were not necessarily associated with stenocardia. At the same time attacks of angina of varying intensity frequently developed without any evidence of either edema or dyspnea. In fact, from this case, it is evident to us that severe attacks of stenocardia can occur even in the presence of a badly damaged left ventricle without producing acute pulmonary edema. The fatal attack was precipitated by intense emotional excitement. In this last attack he was sitting in his chair speaking with friends. He was under decided emotional stress when without warning he complained of

distress in his chest, developed rapid labored asthmatic breathing, grew ashen pale and died immediately.

During an attack, the heart sounds were usually obscured by coarse râles heard everywhere in the chest. His extremities were cold, his skin slightly cyanotic and an expression of extreme anguish developed. He was usually propped up in a semisitting position, hardly able to speak and struggling for every breath. Cardiac dilatation could not be demonstrated by physical or fluoroscopic examination; and there was never any elevation of blood pressure. Occasionally there would be a ten or fifteen point fall in both the systolic and diastolic levels.

For the relief of these attacks many different substances such as amyl nitrate, nitroglycerine, adrenalin, caffeine sodium benzoate and digitalis were tried, but were always found ineffective. Morphine in doses of 1/6 to 1/2 grains was invaluable and often within a few minutes would bring such complete relief that all râles would entirely disappear from the chest and the patient would lie down with comfort. Bed rest for a few days following and digitalis between the at-

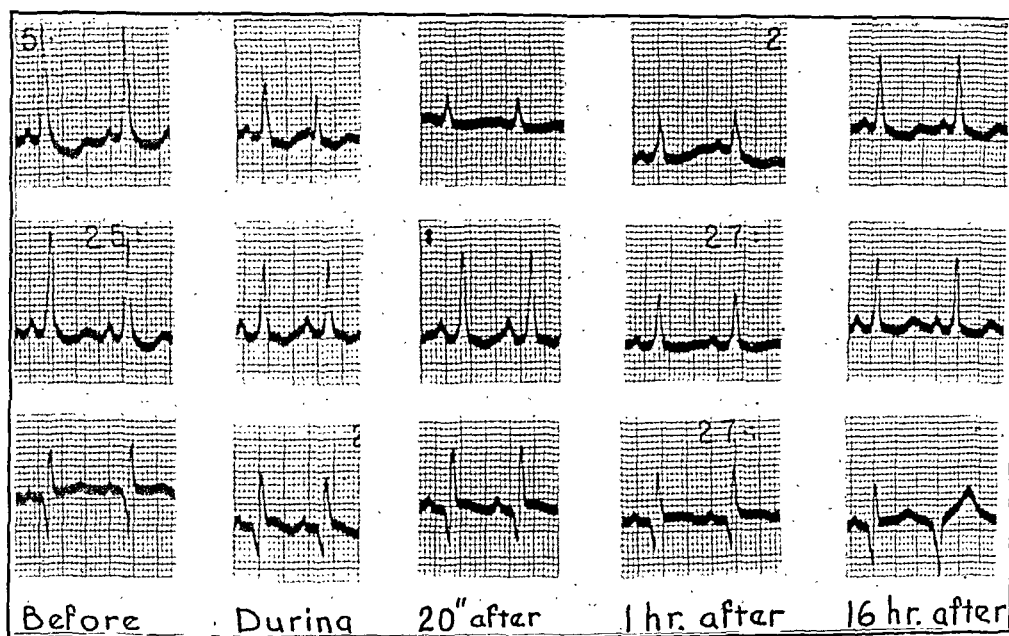


Fig. 1.—Electrocardiographic studies before, during, and after a typical severe attack. Note the marked fall of amplitude almost entirely in the left axis.

tacks seemed effective in preventing their occurrence. Unfortunately, it was impossible to restrict this patient as fully as was desirable. He preferred death to complete invalidism and refused many of the essential physical and emotional restrictions.

*Electrocardiographic studies* were made during a typical attack and the findings will be noted in Fig. 1. In the tracing taken one week before this attack, the marked S-T change, the diphasic  $T_1$  and  $T_2$ , and the slightly increased intraventricular conduction will be noted as indicative of marked coronary disease. At the onset of the attack there is apparent a fall of voltage of the QRS, and increased rate and ventricular extrasystoles. As the attack progresses the height of the R-wave falls very perceptibly, chiefly in Lead I and even after sixteen hours have elapsed, there is evident considerable left ventricular weakening as judged by the fall in height of  $R_1$  and  $R_2$ .

*Autopsy* revealed nothing of importance except in the cardiovascular system. The heart weighed 575 grams. On the posterior wall of the left ventricle, a flabby,

softened, pale area 4.5 by 6 cm. was seen. On sectioning, this proved to be an area of old healed infarction. The wall at this point was only 0.5 cm. in thickness, whereas the wall of the remainder of the left ventricle was 2.5 cm. in thickness. The valves of the heart were normal. The coronary arteries were markedly sclerosed throughout. The wall of the right ventricle appeared quite normal and measured 0.6 cm. in thickness. Fig. 2 shows the large fibrotic area in the left ventricle. There were moderate arteriosclerotic changes in the aorta and in all the smaller arteries throughout the body. The lungs were negative. The kidneys showed a moderate degree of vascular change. It was evident that this marked weakening of the wall of the left ventricle was the basis for the attacks of acute pulmonary edema.

Physical or emotional strain, by increasing the heart rate or elevating the blood pressure, threw an additional load upon the ventricles, already subject to diminished coronary flow. As a result there developed an excessive strain of the damaged and already deficient left ventricle, causing that chamber of the

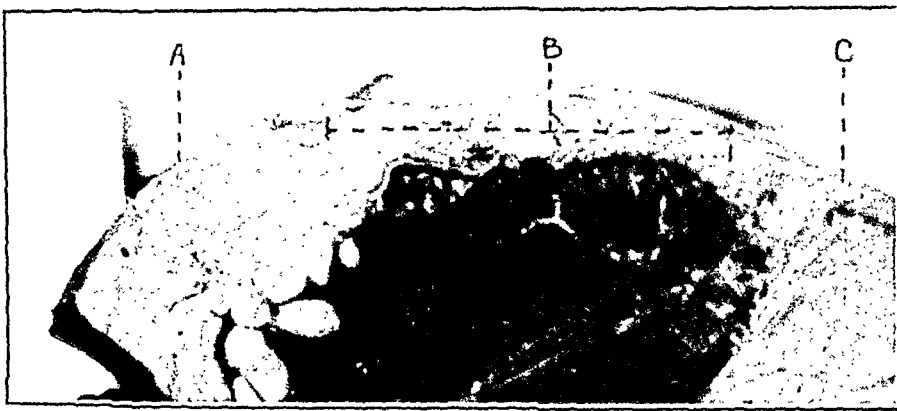


Fig. 2.—Section of heart showing thin, fibrotic area of healed infarct. (A) Lateral wall of hypertrophied left ventricle. (B) Healed infarct in posterior wall of left ventricle. (C) Region of ventricular septum.

heart to lag behind the right ventricle. Arterial output fell behind, pulmonary stasis quickly formed; engorgement and edema resulted. This is in accord with the theory first advanced by Welch and now generally accepted, namely, that the most frequent cause of attacks of acute pulmonary edema is left ventricular failure with ensuing disproportion between right and left chambers.

#### SUMMARY

A case is presented which offers detailed clinical and electrocardiographic study of the nature and causation of attacks of acute pulmonary edema. Autopsy findings substantiate the clinical diagnosis and are further verification of the accepted theory of the cause of this syndrome.

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# BUNDLE-BRANCH BLOCK WITH PERIODS OF NORMAL INTRAVENTRICULAR CONDUCTION: REPORT OF AN UNUSUAL CASE\*

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SEVERE grades of delayed intraventricular conduction are usually permanent and are commonly regarded as indicative of pathological changes of the myocardium. It is not generally recognized that such conduction disturbances may be primarily functional in nature and transitory in occurrence. Herrmann and Ashman,<sup>1</sup> in a recent review of this subject, collected ten cases from the literature in which the intraventricular conduction time was found to vary at different periods of observation. They report in detail eight instances of their own. Three of these were remarkable in that a complete change from bundle-branch block to normal intraventricular conduction occurred during the period of a single cardiac cycle in response to simple maneuvers (breath holding, slight exercise). Wenckebach and Winterberg<sup>2</sup> published tracings obtained from a girl eleven years of age which usually showed partial A-V block with a P-R interval of 0.22, together with altered ventricular complexes which they regarded as indicative of right bundle-branch block. Slight exercise was sufficient to induce a 2:1 A-V block and to cause complete disappearance of the intraventricular conduction delay. At autopsy there was slight structural alteration of the conduction system hardly sufficient in degree to account for the pronounced changes observed in the electrocardiogram. This observation is of particular interest because it indicates that profound intraventricular conduction disturbances may be primarily of a functional nature. It is of course evident that the prognosis in such instances might be favorable.

We wish to describe a patient without cardiac symptoms in whom there occurred abrupt changes from bundle-branch block to normal intraventricular conduction, both spontaneously in combination with transitory 2:1 A-V block, and in the absence of such block, as the result of indirect vagal stimulation.

## CASE REPORT

The patient was an obese white man sixty-six years of age who presented himself for general physical examination. He had no complaints. His hereditary background was good; his parents had lived to old age. He had had uncomplicated scarlet fever at twenty-two years of age, and gonorrhea at twenty. Syphilis was denied. There was no history of rheumatic fever, chorea or tonsillitis. He was fairly abstemious in his habits with the possible exception of a cigarette consumption of 15 daily. He had previously been an executive in a large industrial concern, but of late years had led a life of comparative ease. A recent death in the family

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had taken its toll of worry and unhappiness, but at the time of our examination his equilibrium had returned.

*Examination.*—The patient was an alert individual of sthenic habitus, 5 feet 6 inches tall and weighing 199 pounds. There was no objective evidence of circulatory embarrassment. The radial pulses were synchronous at 76 per minute, the accessible arteries soft, and the blood pressure was 128/74 mm. The apex beat was not palpable. No thrills were felt. Percussion elicited a normal cardiac configuration, but the left border was 1.0 cm. lateral to the midclavicular line in the fifth interspace. The heart sounds were distant and the quality was good except for slight roughening of the first sound at the apex. By fluoroscopy the lungs were normal and the diaphragm was situated rather high in the thorax. The cardiac pulsations were moderately vigorous, the aorta was not widened or elongated, and the retrocardiac space was clear. By orthodiagraphic measurement the right heart border was 5.0 cm. from the midline and the left 11.0 cm., giving a transverse cardiac diameter of 16.0 cm. which was greater than his calculated normal transverse diameter of 14.2 cm. (Eyster's method).

*Laboratory Examination.*—There were no abnormalities of the microscopic and chemical examinations of the blood and urine. The blood Wassermann reaction was negative by the Kahn and Kohmer techniques.

#### ANALYSIS OF ELECTROCARDIOGRAMS

During the examination of this patient a slight transitory pulse irregularity was noted. An electrocardiogram was immediately taken in the usual manner (Fig. 1). The tracing showed a regular auricular rhythm of 75 per minute. The greater number of the ventricular complexes satisfied the criteria for the diagnosis of right bundle-branch block (old terminology), namely, the form of left axis deviation, and slurring, notching, and widening over 0.1 of the QRS groups in all leads with T directed oppositely to the major deflection. In Lead I the third ventricular beat was dropped and the ventricular complex following the fourth P-wave at an interval of 0.2 showed a pronounced change in configuration. The slurring and notching of QRS had disappeared and the QRS interval had narrowed to 0.08. The next two beats showed a return of bundle-branch block configuration after which 2:1 A-V block with constant P-R interval of 0.2 was established, halving the ventricular rate to 37.5 per minute. For the duration of this block, a period of several minutes, the intraventricular conduction disturbance did not recur. With its spontaneous disappearance and return of the ventricular rate to 75 per minute bundle-branch block reappeared (Lead II). In Lead III a dropped beat was recorded followed by one ventricular complex having a normal intraventricular conduction time. Three months later another tracing was obtained. No spontaneous changes in either A-V or intraventricular conduction were recorded. All the ventricular complexes had the bundle-branch block configuration. However, in response to pressure over the vagi in the neck, an abrupt transition to normal intraventricular conduction occurred (Fig. 2). The heart rate before this maneuver was 78.7 beats per minute. As the result of vagal pressure, the rate slowed to 56.6 per minute at which time

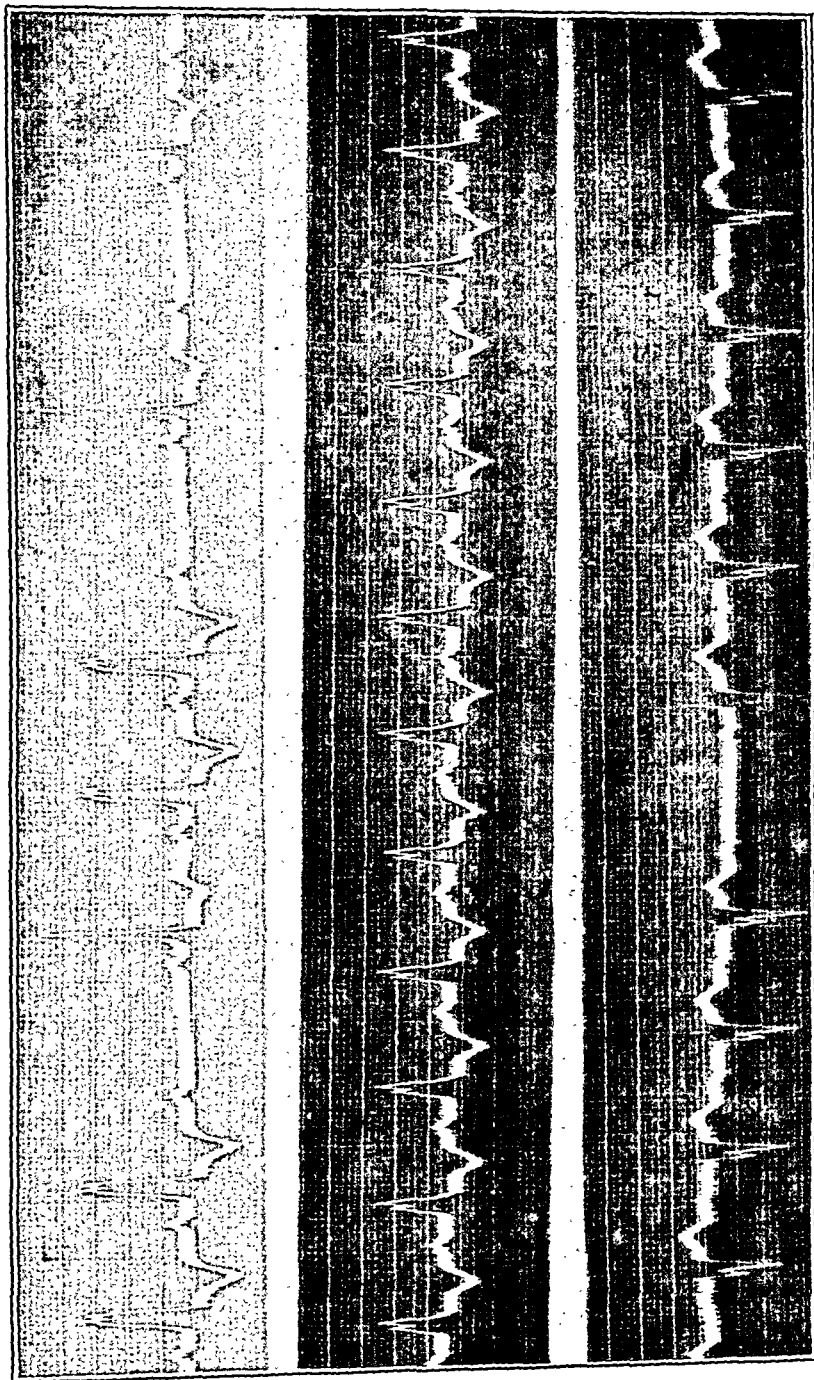


Fig. 1.—Leads I, II and III from above downward. Spontaneously occurring dropped beats and 2:1 A-V block with disappearance of the intraventricular conduction delay.

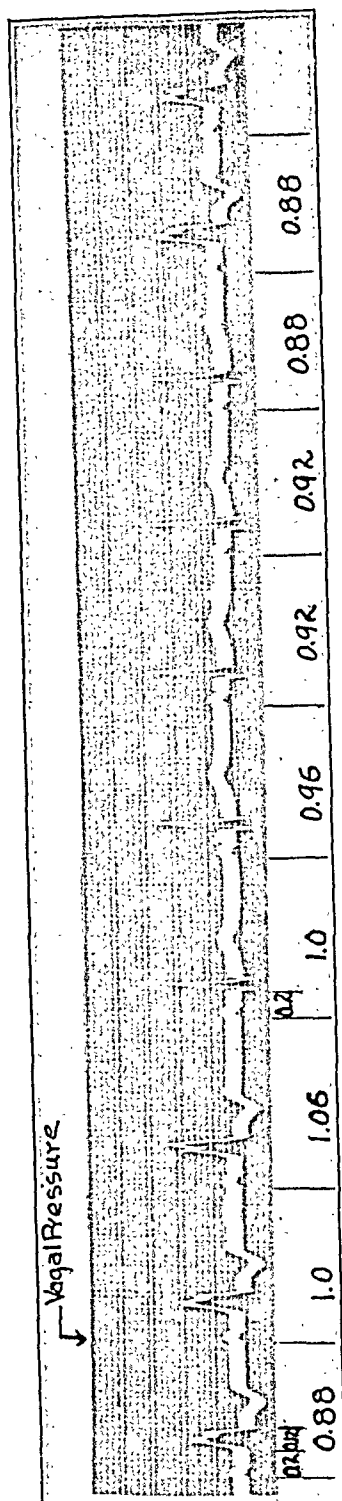


Fig. 2.—Lead II only. Cardiac slowing due to vagal pressure with abrupt cessation and return of the bundle-branch block. The vertical lines beneath the tracing represent the time in seconds. The first transition occurs at the moment of maximum slowing; the second, when the original rate is resumed. P-R interval remains constant at 0.2.

the bundle-branch block disappeared. During five such beats the rate gradually increased to its previous level at which point the bundle-branch block was abruptly reestablished. The P-R interval remained constant at 0.2 throughout.

It should be noted that exercise had no effect upon the intraventricular conduction time.

#### DISCUSSION

The classification of bundle-branch block as to type is of much theoretical interest. The reader is referred to the paper of Herrmann and Ashman for an excellent discussion of the nature of partial bundle-branch block and of the diagnostic criteria for its identification as to type.

In this instance the classification of the block could not be made from the first tracing alone. The fact that the A-V block was manifestly of type 2, shown by the dropped beats and establishment of 2:1 rhythm without prolongation of the P-R interval, gave no information as to the exact type of conduction disturbance present in the bundle. In the second tracing, however, there was recorded, as in the first three cases of Herrmann and Ashman, an abrupt transition within the space of a single cardiac cycle from bundle-branch block to normal intraventricular conduction. This makes it clear that the bundle-branch block was definitely of type 2 and as such is the fourth instance of its kind to be reported.

The fact that the transition in this instance occurred only with cardiac slowing would seem to indicate that the bundle-branch block was primarily the result of fatigue of the conduction system and that the depressed tissue was probably of very small extent. Such a conception is borne out by the fact that the patient had neither cardiac symptoms nor a clinically diagnosable heart lesion beyond a moderate hypertrophy. There seems furthermore to have occurred in this patient an improvement in the physiological state of the conduction system over a period of three months as evidenced by the disappearance of the spontaneously occurring 2:1 A-V block. It does not seem unreasonable to hope that in time the intraventricular conduction disturbance may likewise disappear. We shall watch the future course of this patient with great interest.

#### SUMMARY

The electrocardiographic tracings taken from a sixty-six-year-old man who had no cardiac symptoms showed a typical bundle-branch block which abruptly disappeared with the spontaneous occurrence of 2:1 A-V block, and which disappeared after cardiac slowing, the result of indirect vagal stimulation.

This is the fourth instance of proved type 2 bundle-branch block to be reported.



It is believed that the conduction disturbance in this instance was primarily the result of fatigue of the bundle and that the depressed tissue was small in extent.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Hamilton, W. F., Spradlin, M. C., and Saam, H. G.: *An Inquiry Into the Basis of the Acetylene Method of Determining the Cardiac Output.* *Am. J. Physiol.* 100: 587, 1932.

An attempt is made to evaluate the acetylene method of determining the cardiac output. The authors believe that while there seems to be an agreement between the acetylene method and the Fick procedure in determining the cardiac output that the acetylene method produces readings which are too low and that the source of error lies in the difficulty in determining the samples of air before the acetylene gas returns to the rebreathing chamber.

Kouwenhoven, William B., Hooker, Donald R., and Langworthy, Orthello R.: *The Current Flowing Through the Heart Under Conditions of Electric Shock.* *Am. J. Physiol.* 100: 344, 1932.

The purpose of the experiments described in this paper was to ascertain the proportionate value of total electric current which actually flows through the heart when contact at various points on the body is made with the circuit and to determine the minimum current necessary to establish ventricular fibrillation. Dogs completely anesthetized with morphine and ether were used as experimental animals because the ventricles of the dog's heart are readily thrown into a permanent state of fibrillation by the application of relatively weak currents as is assumed to be the case in man.

It was found that 9 or 10 per cent of the total current passing through the body flows through the heart for a current pathway parallel to the body axis. When the current flows transversely, only about 3 per cent passes through the heart. Thus, as far as the heart is concerned, fibrillation will be produced by a much smaller total current flowing from the upper to the lower extremities than between the forelegs.

In most industrial accidents the current path is from the right hand to the feet and under these conditions the heart carries a greater proportion of the total current than when contact with the circuit is made at any other location on the body.

Jones, Noble W., and Newsom, S. J.: *Experimentally Produced Focal (Dental) Infection in Relation to Cardiac Structure.* *Arch. Path.* 13: 392, 1932.

In this paper the authors present the results of their study of the following problems: (1) the relationship between experimentally produced focal (dental) infection and cardiac hypertrophy in dogs; (2) the relative effects of exercise on the hearts of such infected and noninfected dogs; (3) the reliability of the various means of expressing cardiac hypertrophy; and (4) other pathological changes cardiac and extracardiac found in the experimental animals. Dental abscesses were produced by introducing streptococcus material through an opening in the root canal of the dogs. These dental abscesses could be demonstrated in all inoculated dogs. The hearts showed constantly very small vegetative or verrucose

mitral and/or aortic endocarditic lesions, patchy parenchymatous degeneration, nuclear changes, increase in the diameter of the muscle cells and a slight round cell infiltration.

Positive relationship between experimentally produced focal dental infections and cardiac hypertrophy as measured by diameter of muscle cells was noted. Direct measurement of diameters of cardiac muscle fibers under the experimental conditions was a more reliable criterion of cardiac hypertrophy than ratios of heart weight to body weight or of heart weight to body surface area.

Stress and strain in the absence of focal infection did not affect the gross or the microscopic characteristics of the heart.

Schultz, M. P., and Swift, Homer F.: Reaction of Rabbits to Streptococci: Comparative Sensitizing Effect of Intracutaneous and Intravenous Inocula in Minute Doses. *J. Exper. Med.* 55: 591, 1932.

Rabbits were rendered very hypersensitive by relatively small doses of green streptococci given intracutaneously and somewhat less hypersensitive by similar doses of heat killed vaccine prepared from hemolytic streptococci. Animals receiving the same doses intravenously gave upon subsequent testing lesions slightly more marked than normal controls, but these lesions were qualitatively hard and nodular compared with the large edematous lesions in the cutaneously sensitized group.

There was no parallelism between the degree of cutaneous or ophthalmic hypersensitivity and agglutinin titer in the blood serum. It is believed that bacterial hypersensitivity to whole streptococci appears to depend more upon previously induced focal infection than upon circulating antibodies.

McEwen, Currier: Cytologic Studies on Rheumatic Fever. 1. The Characteristic Cell of the Rheumatic Granuloma. *J. Exper. Med.* 55: 745, 1932.

Scrapings of subcutaneous nodules from 10 patients with rheumatic fever were examined microscopically after being stained with supravital dyes. From the uniform results obtained the following conclusions have been drawn: (1) Supravital staining of cells from these lesions gives information unobtainable with ordinary histologic methods. (2) The scrapings show a great predominance of certain cells almost entirely devoid of phagocytic power. All the supravital stained preparations showed small masses of tissue composed of many cells lying in a fibrillar mesh work and of wavy fibrils such as occur in similar preparations of tendons or deep fascia. Only at the margins of these masses, however, could the cells be clearly distinguished. Lying between the bits of tissue were large numbers of these same cells which because of their isolated positions could be more accurately studied. All transitions in the type of the cells were seen, ranging from small cells about the size of intermediate lymphocytes to spindle-shaped cells and large, multinucleated giant forms. The predominating cell was from 15 to 20 microns wide by 20 to 30 microns long. The small cells, however, were sometimes only 8 x 15 microns in diameter, while the multinucleated cells measured 32 x 77 microns. The shape was usually oval, but many of the cells had pointed processes at one end which were often at a sharp angle to the rest of the cell.

The cell membrane in freshly studied preparations was very indistinct but more definite in those kept in the icebox for forty-eight hours. The cytoplasm had a coarse, ground glass appearance, and its pale yellowish gray color showed it to be slightly basophilic. The nucleus was oval and large, almost filling the small cells but occupying relatively less of the larger ones. In sharp contrast to the vague cell outline, the nuclear membrane was extremely distinct. The

nuclear background had almost the same appearance as the cytoplasm, but the ground glass markings were coarser and the basophilia slightly greater. The nucleus and cytoplasm were so similar that if it had not been for the sharply outlined nuclear membrane it would have been difficult to distinguish between them. One or two nucleoli were usually present. Definite mitochondria were never seen although in a few cells a faint suggestion of minute, pale blue dots was noted. A striking contrast to this was observed in the case of lymphocytes present in small numbers in many of the preparations.

The failure of the cells to take up neutral red was their most striking characteristic which distinguishes them from monocytes, epithelioid cells and clasmatoctocytes; hence they differ from the essential cells of tuberculosis and experimental syphilis. These differences are probably of a functional and developmental rather than of a genetic nature. (3) The cells probably arise from the undifferentiated mesenchymal elements of loose connective tissue, although it is possible that endothelial cells take part in their formation in some instances. (4) Since there is little doubt that the subcutaneous rheumatic nodules are pathologically identical with rheumatic granulomata elsewhere in the body, these conclusions are considered applicable also to the Aschoff body cells of the myocardial submiliary nodules.

Hamilton, Joseph E., Lichty, Joseph S., and Pitts, William R.: *Cardiovascular Response of Healthy Young Men to Postural Variations at Varied Temperatures*. *Am. J. Physiol.* 100: 383, 1932.

Tilting subjects from a horizontal to a vertical position head up, has certain effects upon the cardiovascular response at all temperatures. The systolic pressure curve remains nearly level, while the diastolic pressure steadily approaches it as the vertical position is neared. The resulting pulse pressure shows a physiological narrowing. The pulse rate rises steadily to a maximum at 80 or 90 degrees. When the subjects are returned to the horizontal position, the pulse pressure immediately widens in excess of the reading at the commencement of the experiment. The pulse rate rapidly drops.

The effects of high temperature are as follows: The systolic pressure tends to fall slightly at the higher temperatures, but since the diastolic pressure curve is lowered more than is the systolic pressure curve, the pulse pressure is wider than at room temperature. The pulse rate increases directly as the temperature. In this study there were three instances of fainting at 120° F. and one instance at 130° F. all occurring above the angles of 50°.

Tilting experiments were carried out in which the subject's ventilation was measured by means of a special spirometer. The results show a steady increase in ventilation as the subject is tilted from horizontal to vertical, a mechanism which by its aspirating effects helps to return the blood to the right heart in erect positions.

In regard to a scoring system of cardiovascular efficiency, the authors feel that the data obtained in these experiments justify only a general estimate of any given response such as "good," "fair," or "poor."

Turley, F. C., and Harrison, T. R.: *Respiratory Measurements as Affected by Smoking and by Athletics*. *Am. J. M. Sc.* 183: 702, 1932.

Respiratory measurements were made on a group of 75 medical students and on 13 football players in active training with the idea of determining whether persons who smoke excessively are more short winded than individuals who do not smoke. As a result of these measurements of ventilation, the following conclusions may be drawn. "Heavy smoking," twenty cigarettes or more a day

for several years, does not significantly diminish the respiratory efficiency in the performance of mild and moderately severe exercise. Athletic individuals are not much more efficient than sedentary persons in the performance of mild exercise but are considerably more efficient in carrying out moderately severe exercise. Individuals who have once been highly trained remain extremely efficient in their breathing for a number of years after giving up active training provided they take fairly regular exercise.

Weiss, Soma, Robb, George P., and Ellis, Laurence B.: *The Systemic Effects of Histamine in Man With Special Reference to the Responses of the Cardiovascular System.* Arch. Int. Med. 49: 360, 1932.

A study of the systemic effects of histamine in man and a discussion of the physiological and pathological rôle of histamine based on these observations are presented.

Following the single or continuous intravenous administration of histamine, the latter is converted promptly into ineffective substances in the human body. The persistence of the action of histamine in man is of but a few minutes' duration. With uniform intravenous infusion, the bodily changes induced are practically stationary. The minimal effective amount of histamine base in man is about 0.003 mg. per minute corresponding to a concentration of about 1:2,000,000,000 parts in the circulating blood. The maximal amount of histamine base, administered intravenously, that produces toxic manifestations is 0.15 mg. per minute.

Relatively small amounts of histamine cause a depression of the T-waves of the complexes of the normal electrocardiogram. With elevation of the dosage, the degree of depression increases until the T-wave may become inverted. After a single intravenous dose, the change in the shape of the T-wave is instantaneous with the arrival of histamine in the coronary circulation, and within one minute there is a tendency to return to the normal shape. Changes in the T-waves are not associated with any symptoms or signs referable to the heart. Histamine in amounts up to toxic doses in observations of two hours' duration fails as a rule to produce any lowering of the systolic arterial blood pressure. The diastolic arterial blood pressure shows a tendency to fall, but in numerous instances it also remains unaltered. With increasing amounts there is a progressive rise in the cardiac rate. The venous pressure is either unaltered or slightly elevated.

The effect of histamine on the cutaneous blood vessels is not uniform. The most characteristic effect is a dilatation of the venules and small veins. This effect is frequently independent of the dilator effect on the arterioles. In one group of subjects, even toxic doses fail to produce a dilatation of the arterioles as judged by the cyanotic flush and lack of elevation of the surface temperature of the skin. In a second group of subjects the arteriolar dilatation develops when a larger dose rather than one that produces a dilatation of the venules is administered. In a third group the dilatation of the arterioles and venules occurs simultaneously.

As judged from the degree of elevation of the pressure in the minute vessels of the skin, the arteriolar dilatation following large intravenous doses of histamine is slight as compared with that following the local intra-cutaneous application of histamine base in a solution of 1:3,000. The different types of observations presented offer conclusive evidence that the minute cerebral vessels of man respond to histamine with conspicuous dilatation. A certain parallelism exists between the sensitivity of the facial and the cerebral vessels to histamine. In a number of instances the cerebral vessels were even more sensitive than the

facial vessels, and cerebral arteriolar dilatation followed the intravenous administration of such small amounts as 0.003 mg. of histamine base.

The cardiac output per minute following the intravenous infusion of from 0.02 to 0.03 mg. of histamine base per minute increases by an average of 1.5 liters or to 20 per cent above the normal value. Simultaneously there is a slight fall in the stroke volume. The mean velocity of blood flow shows a slight but distinct increase. The basal metabolism becomes elevated and may reach values 50 per cent above the normal. There is a slight fall in the respiratory quotient.

A study of the chemical constituents and certain physical characteristics of the blood together with its hemoglobin combining power indicates that with the administration of histamine, transudation of small amounts of whole plasma occurs. This amount is too small to be demonstrated by the measurements of the total blood volume with the dye method. Histamine produces no demonstrable changes in the pulmonary ventilation or in the state of the bronchioles of normal persons, but has a definite bronchial constrictor effect on patients with bronchitis, bronchial asthma, emphysema and cardiac asthma.

*Histamine when administered orally in massive doses is ineffective; hence its rôle in intestinal intoxication is highly questionable.*

Evidence is presented that during the administration of histamine substances are formed or vasomotor reflexes develop which act antagonistically to histamine. The degree of peripheral vascular dilatation in man induced by histamine is not marked, and the distribution is not widespread. The vasodilator effect of histamine is promptly counteracted by an increase in the cardiac output and in other regulatory functions. A certain parallelism exists between the circulatory responses that follow exercise and those that follow the injection of histamine but this parallelism is incomplete. The vascular and other bodily responses induced by histamine in man differ fundamentally from those observed in anesthetized cats and in patients with traumatic shock. The rôle of histamine in traumatic shock is therefore considered doubtful.

Shelburne, Samuel A., Blain, Daniel, and O'Hare, James P.: *The Spinal Fluid in Hypertension.* J. Clin. Investigation 11: 489, 1932.

A study of 50 cases of hypertensive disease showed 21 to have increased intracranial pressure. Papilledema and increased intracranial pressure occur more frequently with renal failure but are also found where renal function is normal. Papilledema was almost always associated with increased intracranial pressure.

Headache is more frequent in the presence of increased intracranial pressure and papilledema but occurs without either one. The results indicate that lumbar drainage for relief of headache is not justified. Increased intracranial pressure seems more often associated with high diastolic blood pressure, but the authors feel that both are probably the result of some common factor and neither is caused by the other. The cause of increased intracranial pressure is not accounted for in 50 per cent of our cases which have neither renal insufficiency nor increased venous pressure.

Heyl, Arthur F.: *Auricular Paroxysmal Tachycardia Caused by Digitalis.* Ann. Int. Med. 5: 858, 1932.

The author reports the case of an adult male past middle age with hypertension and congestive heart failure in whom it was observed that digitalis which gave him relief from dyspnea, cough, edema and passive congestion at the same time induced auricular paroxysmal tachycardia followed by a two to one block in which the abnormal auricular mechanism prevailed. These abnormal rates

and rhythms occurred only as the result of digitalis administration. No other toxic symptoms due to digitalis ever occurred even with full calculated doses.

Various methods, such as effort, deeply held inspirations, forced coughing and amyl nitrite inhalations, were utilized in an attempt to induce the attacks both in the presence and in the absence of digitalis administration. When no digitalis was being administered they were consistently unsuccessful.

Various attempts were made to ascertain the effects of vagus stimulation. While he was free from digitalis, external vagus stimulation did not produce any change in the cardiac rate or rhythm nor any electrocardiographic variations. Neither did digitalis alone even in full dosage slow the rate as would have been true had it acted directly on the vagus.

The author points out that graphic methods are especially favorable for diagnosis in patients with sinus tachycardia, particularly in those who need and are receiving digitalis. In this instance even mild doses repeatedly resulted in *auricular paroxysmal tachycardia with or without a two to one block with a rapid ventricular rate* which without electrocardiographic control might naturally have led to the futile use of more digitalis and increased toxicity in an effort either to slow the ventricular rate or to prevent the often recurring "clinical" auricular paroxysmal tachycardia.

**Duff, G. Lyman:** Medial Degeneration in the Aorta of the Rabbit Produced by Diphtheria Toxin. *Arch. Path.* 13: 543, 1932.

Successive intravenous injections of diphtheria toxin in suitable quantities produce in rabbits severe medial degeneration of the aorta and its large branches within from eight to fourteen days. Damage to the arteries is probably the result of the direct toxic action of diphtheria toxin on the media.

The changes in the media are most marked in the arch and thoracic portion of the aorta resulting in thinning of the arterial wall, dilatation and the formation of aneurysmal sacs. With the establishment of calcification, transverse fissures appear on the intimal surface. The lesion commences in the middle third of the media primarily as a cloudy swelling, degeneration and necrosis of muscle fibers. Fatty changes occur in the process at least in its later stages. Elastic fibers, slightly later, also undergo degeneration with the loss of elasticity and the development of stiffness and rigidity even before the appearance of calcification. Calcification is first seen as a finely granular deposit in the debris of degenerated muscle fibers but later involves also the elastic fibers and becomes most prominent in them. These changes were found in young animals and are different from those which are observed in older animals.

Direct application of these results to human diphtheria is rather precarious. One might suggest, however, the possibility of a relationship. Many investigators have questioned the statement that damage to the heart alone is sufficient to account for the circulatory collapse in rapidly fatal cases of diphtheria. Accordingly, damage to vasomotor centers has been invoked as a factor contributing to this collapse. It would seem at least possible from the present experiments that direct damage to peripheral arteries may also have a bearing on this phenomenon.

**Alstead, Stanley:** The Electrocardiogram in Diphtheria. *Quart. J. Med.* 1: 277, 1932.

The object of this investigation was to attempt to define the changes commonly seen in the electrocardiogram in the course of diphtheria, to correlate them to the clinical condition and to assess the value of this form of investigation in a fever hospital.

It was found that while a large proportion of cases having mild myocarditis are undetected by clinical methods, such cases become comparatively rare in the moderate and severe types of diphtheria. Hence for practical purposes the character of the heart sounds is usually a sufficiently accurate guide to the state of the myocardium.

Of the various physical signs in the heart taken to indicate myocarditis in diphtheria, the most valuable as confirmed by simultaneous electrocardiographic records are: (a) progressive softening of the first heart sound at all areas especially the mitral and aortic areas; (b) the character of the cardiac impulse at the apex and movement of the apex beat to a position farther away from the midline; (c) splitting of the first mitral sound producing a triple rhythm.

Serial electrocardiographic records show that with the onset of diphtheritic paralysis there is in a considerable proportion of cases a simultaneous relapse in the condition of the heart. This fact is much less frequently observed when clinical methods alone are employed. Although gross degeneration of the heart muscle and specialized conducting system are frequently shown by the electrocardiograph during diphtheria these lesions are mostly transient. Complete heart block is by far the commonest lesion associated with circulatory collapse ending fatally, but complete block is probably only a contributory factor in a condition characterized by widespread changes in the circulatory system.

The severity of the cardiac lesion is usually proportional to the severity of the toxemia when specific treatment is commenced. There are, however, cases in which neither the clinical nor the electrocardiographic abnormalities are sufficient to account for the state of impending circulatory collapse which is often seen in diphtheria.

It is concluded that the electrocardiograph is a valuable means of estimating the severity of diphtheritic myocarditis and the only means of accurate diagnosis of conductive lesions in the majority of cases. The clinical signs which are most closely related to the electrocardiographic findings are those dependent on cardiac function. The significance of persistently abnormal heart sounds can be safely estimated by the electrocardiogram and the patient's response to effort considered together.

**Salley, S. M.: An Unusual Atropin Effect on Ventricular Tachycardia.** *Am. J. M. Sc.* 183: 456, 1932.

A case of coronary thrombosis was observed showing ventricular tachycardia with a rapid ventricular rate. The ventricular rate was frequently slowed by increasing doses of quinidin to 110 or 115, but the tachycardia could not be abolished. Immediately following one dose of 0.002 gm. of atropin sulphate this abnormal mechanism disappeared uncovering complete heart block with a slow idioventricular rhythm. It is believed that the circus movement was broken up by atropin through its paralyzing effect on the vagus.

**Nathanson, M. H.: Coronary Disease in 100 Autopsied Diabetics.** *Am. J. M. Sc.* 183: 495, 1932.

An analysis of 100 autopsies upon diabetics shows an incidence of 41 per cent of severe coronary disease. Above the age of fifty years the incidence is 52.7 per cent as compared with 8 per cent in an even larger series of nondiabetics of the same age. The frequency of coronary disease is almost as high in the female as the male.

The incidence of hypertensive hypertrophy of the heart indicates that hypertension is only slightly more frequent in the diabetics than the nondiabetics. In diabetics with gangrene the incidence of coronary disease is higher than



in the uncomplicated cases. The essential cardiac lesion of diabetes is coronary sclerosis. Other types of cardiac disease are of relatively rare occurrence. The etiological relationship between diabetes and arteriosclerosis is discussed.

**Brown, Herbert H.: Tooth Extraction and Chronic Infective Endocarditis.** Brit. M. J. 1: 796, 1932.

The danger of extracting teeth with apical streptococcal infection is a real one, and the author feels convinced that the danger is increased if local anesthesia by infiltration of the gum is made use of. It is not feasible to estimate beforehand the patient's resistance to the infecting organism and cultures often cannot be made until the tooth is extracted.

It is suggested that as a precaution, especially in the case of an individual already suffering from valvular disease or one who may seem for other reasons to be liable to have a weak resistance, to extract one tooth only in the first instance under a general anesthesia. Under these conditions, a culture may be made and, if possible, the patient's blood may be tested for bactericidal power against the organism.

**Brown, George E.: Erythromelalgia and Other Disturbances of the Extremities Accompanied by Vasodilatation and Burning.** Am. J. M. Sc. 183: 468, 1932.

A series of 81 patients whose major complaint was burning in the feet or hands was studied to determine the relationship, if any, of the burning distress to the surface temperature of the affected part, the variation in surface temperature and local symptoms in relation to posture, exercise and exposure to heat and cold: to determine in a small group of patients by the method of inducing fever, by injection of foreign proteins, the thresholds for perception of the burning sensation, in relation to surface temperature regions in which the burning was felt, and whether or not the patients could be relieved in cases in which the burning distress of a paresthetic type was present by inducing spinal anesthesia to the point of total analgesia in the feet.

The author discusses the difficulties in establishing a diagnosis of this disease. Four fundamental criteria which are essential are mentioned. The methods of study to distinguish between the different conditions in which burning extremities occur are outlined. The treatment of this condition remains unsatisfactory.

**Pearse, Herman E., and Morton, John J.: The Blood Pressure in the Arteries of the Extremities in Normal Subjects and in Patients With Peripheral Vascular Disease.** Am. J. M. Sc. 183: 485, 1932.

The effect of altering the position of a limb on the blood pressure of the peripheral arteries has been studied. It was found that alteration of an extremity lowered the blood pressure while its depression raised the intraventricular pressure. These results correlated with the theoretical hydrostatic change of such a maneuver.

In peripheral vascular lesions it is essential to know the condition of the main arteries as well as that of the arteriolar and subpapillary branches. The vasoconstrictor influence upon the latter structures is demonstrated by a skin temperature response to known agents. The state of the main vessels can only be determined by estimation of the perceptible pulse or by oscillography.

In the past the Pachon instrument has been the standard for oscillographic determinations. The Tycos recording sphygmomanometer has the advantage of giving an accurate, permanent calibrated record for this purpose. The use of this instrument with the special cuffs devised is considered desirable not only to determine the condition of the vessels in disease but also to study vascular physiology.

## Book Reviews

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DISEASES OF THE CORONARY ARTERIES (Myocarditis). By Don C. Sutton and Harold Lueth. The C. V. Mosby Company, Saint Louis, 1932, pp. 164.

This volume is evidence of the increasing interest in arteriosclerotic heart disease (one regrets that the authors retain the term "Chronic myocarditis"), and while it does not add new facts to our knowledge it brings together, especially for the clinician, many recent observations. The book is generously illustrated and contains many references, quotations, and case reports; it gives evidence, however, of hasty preparation. The interpretation of several of the electrocardiograms is open to serious question and some of the quotations fail to illustrate the subject under discussion. The book is evidently the result of independent investigation and wide reading, and the bibliography alone would repay careful study. *E. H.*

SEMIOLOGIA DE LA ONDA T DEL ELECTROCARDIOGRAMA Y SU INTERPRETACION CLINICA. By Antonio Battro. Buenos Aires, 1931, Sebastian de Amorrotu.

This monograph of 120 pages with 66 illustrations is concerned solely with the T-wave of the electrocardiogram, its form and significance in tracings from persons with normal hearts and in those from patients with various types of heart disease. There is also a discussion of the prognostic value of changes in the T-wave. It is a careful and detailed study of a limited field. *E. H.*

KLINISCHE ELEKTROKARDIOGRAPHIE MIT EINEM GRUNDRISSE DER ARHYTHMIEN. By Dr. Wilhelm Dressler, assistant at the Herzstation in Vienna. With an introduction by Prof. Dr. C. J. Rothberger. Second, revised edition, with 118 illustrations. Berlin and Vienna, 1932, Urban & Schwarzenberg.

This volume was written to supply the need in the German clinics for a clinical book on electrocardiography.

The introduction by Professor Rothberger emphasizes the importance of this need, and the fact that such books have appeared in English and American literature for many years and have been of great educational value to the general practitioner.

The book follows very closely the general scheme of similar books published by American authors. It fulfills its purpose in that it gives the general practitioner an excellent idea of what the electrocardiogram is, and what information it may convey.

The section on the electrocardiographic evidences of myocardial disease is unusually good. Unfortunately the author at times gives only single leads to illustrate the cardiac disturbances. The time marker also is missing from many of the curves, and in others it is very indistinct.

Dr. Dressler still adheres to the original description of right and left bundle-branch block. The recent interpretation of bundle-branch block will doubtless be incorporated in the next edition.

The clinical manifestations of the various cardiac disturbances are given in rather sketchy fashion and there is no bibliography.

*M. A. R.*

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## Original Communications

### THE INCIDENCE AND SIGNIFICANCE OF THE DEEP Q-WAVE IN LEAD III OF THE ELECTROCARDIOGRAM\*

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IN 1926, Wilson<sup>1</sup> stated that a deep Q-wave in Lead III is an important electrocardiographic finding following coronary occlusion. Parkinson and Bedford<sup>2</sup> and Levine<sup>3</sup> also noted this wave in some of their cases of coronary occlusion. Pardee's work,<sup>4</sup> however, was the first to arouse widespread interest in the Q-3 wave. His contributions include (a) the proposal of criteria to separate significant from nonsignificant Q-3 waves, and (b) a study of the incidence of presumably significant Q-3 waves in clinical material. His conclusions include the following statements:

"The finding of a large Q-3 indicates disease of the left ventricle, so that the right ventricle predominates during the spreading of the contraction in spite of the left axis deviation or normal axis."

"The majority of such records are obtained from patients with the anginal syndrome, but certain patients with myocardial fibrosis and congestive failure, certain patients with rheumatic heart disease, especially with pericarditis, and a few with hypertension will give such records. Certain patients who have cardiac symptoms but no definite evidence of cardiac disease have been found to show this large Q-3."

"The occasional finding of a large Q-3 in normal hearts may be due to an unusual distribution of the branches of the A-V bundle, and a high position of the diaphragm may be a contributing factor."

In this paper, the material at our disposal has been analyzed in an attempt to evaluate the importance of Q-3. We have adhered to the criteria for a significant Q-3 proposed by Pardee.

Our cases have been divided arbitrarily as follows:

- I. A. Seven hundred and nine presumably normal college students.
- B. One hundred and seventeen college athletes.

\*From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

- II. Five hundred cases from the wards and cardiovascular section. The only criteria for inclusion in this group included (1) adequate records, (2) unquestionable evidence of cardiovascular disease.
- III. Nineteen hundred unselected electrocardiograms from the files of the Cardiographic Laboratory.
- IV. One hundred and sixteen cases having the anginal syndrome.
- V. One hundred and forty-five corporation executives.\*
- VI. Twenty-five pregnant women.

There is no overlapping among Groups I, III and VI. Cases in Groups II, IV and V which happened to be studied within the time period of the material in Group III are included.†

*Group I.*—The records of 709 apparently normal college students were made available by Dr. Francis Clark Wood. In this group, not a single significant Q-3 was found. There were nine tracings in which the amplitude of a Q-3 was sufficient to satisfy Pardee's requirement in this respect, but they did not fulfill certain of his other criteria, since all showed either right axis deviation or a tendency toward this deviation.

The records of one hundred and seventeen athletes of the University of Pennsylvania were also made available by Dr. Wood. This group included members of the crew, the football, soccer and lacrosse teams. One significant Q-3 wave was found. The recorded physical examination of this individual disclosed a notation of systolic and diastolic murmurs at the apex. Through an error in filing this record had been placed in the normal group. Another tracing showed a Q-3 wave of sufficient depth, but there was a tendency toward right axis deviation.

*Group II.*—The electrocardiograms of 500 patients with definite cardiovascular disease were examined. This group included the usual types of patients seen in the ward and the out-patient cardiovascular clinic.

There were 31 (6 per cent) significant Q-3 waves in this group. The etiological diagnosis of the patients showing a significant Q-3 wave were:

- I. Rheumatic type, 3 cases: (a) mitral stenosis, 1; (b) mitral stenosis and aortic insufficiency, 2.
- II. Hypertension and/or arteriosclerosis, 15 cases.
- III. Syphilis, 8 cases: (a) aortitis, 5; (b) aortitis and aortic insufficiency, 2; (c) aneurysm, 1.
- IV. Thyrotoxic heart, 1 case.
- V. Etiology undetermined, 4 cases.

The youngest patient showing a significant Q-3 was thirty-two years of age, the oldest seventy-two. Five cases (16 per cent) were found to

\*The data in this group were obtained from routine health examinations by Dr. T. Grier Miller and one of us.

†Group III represents a cross section of material from all sources subjected to electrocardiographic study in this Clinic. Time periods were chosen at random and in each period tracings were taken consecutively. No more than one tracing of any one patient was included.

have the anginal syndrome. In two cases, one arteriosclerotic and the other of unknown etiology, the hearts were transversely inclined by a high diaphragm, and both showed definite evidence of cardiovascular disease.

The electrocardiograms in 18 of the 31 cases with significant Q-3 waves were otherwise normal; 8 showed T-wave changes; 4 slurred QRS complexes; and 1, complete heart-block.

*Group III.*—Nineteen hundred unselected electrocardiograms taken from the files were examined in an attempt to determine the general prevalence of a significant Q-3 wave among the types of material ordinarily studied in our cardiographic laboratory. In contrast to Group II, which consisted of ward and clinic patients, this group also included private patients. There were 78 (4.1 per cent) significant Q-3 waves in this group. Of these, 40 (5.2 per cent) were found among 768 private patients and 38 (3.44 per cent) among 1132 ward and clinic patients. The clinical classification of this group is shown in Table I.

Of the 75 patients whose records were available, or concerning whom information was obtainable from the referring physician, 63 (84 per cent) could be definitely classified as having cardiovascular disease, and of this number, 22 (41.5 per cent) had a history of either angina pectoris or coronary occlusion, or both.

TABLE I

CLASSIFICATION OF THE 78 CASES FROM GROUP III EXHIBITING A DEEP Q-3 WAVE

|                 | NUMBER | ANGINAL SYNDROME |                    | HYPERTENSION AND/OR ARTERIOSCLEROSIS* | RHEUMATIC TYPE | CARDIOVASCULAR SYPHILIS | HYPERTHYROIDISM | MYOCARDIAL DISEASE ETIOLOGY UNKNOWN | CARDIOVASCULAR DISEASE DOUBTFUL | EVIDENCE OF CARDIOVASCULAR DISEASE, NEGATIVE OR INSIGNIFICANT | NO RECORDS AVAILABLE EXCEPT ELECTROCARDIOGRAM |
|-----------------|--------|------------------|--------------------|---------------------------------------|----------------|-------------------------|-----------------|-------------------------------------|---------------------------------|---|---|
|                 |        | ANGINA PECTORIS  | CORONARY OCCLUSION |                                       |                |                         |                 |                                     |                                 |   |   |
| Private         | 40     | 12               | 6                  | 8                                     | 1              | 0                       | 0               | 3                                   | 4                               | 3   | 3   |
| Ward and clinic | 38     | 2                | 2                  | 11                                    | 6              | 3                       | 4               | 5                                   | 1                               | 4   | 0   |
| Total           | 78     | 14               | 8                  | 19                                    | 7              | 3                       | 4               | 8                                   | 5                               | 7   | 3   |

\*Without the anginal syndrome.

In this group, the marked predominance of angina pectoris and coronary occlusion in the private cases as contrasted with the ward and clinic cases is striking. It is noteworthy that rheumatism, syphilis and goiter were found more frequently among the ward and clinic cases.

TABLE II  
CLINICAL DATA IN THOSE CASES EXHIBITING A DEEP Q-3 WAVE WHICH WERE CLASSED IN TABLE I AS NEGATIVE OR DOUBTFUL

| NEGATIVE OR INSIGNIFICANT FINDINGS |  |   | EVIDENCE OF CARDIOVASCULAR DAMAGE INCONCLUSIVE |   |   |
|------------------------------------|--|---|--|---|---|
| AGE                                | CARDIAC SYMPTOMS AND FINDINGS  | COMMENTS  | AGE  | CARDIAC SYMPTOMS AND FINDINGS   | COMMENTS  |
| 73                                 | No cardiovascular symptoms; no positive physical findings except extrasystoles. Heart normal in size.  | Two complete examinations more than a year apart.   | ABOUT 50                                       | Precordial pain; low T-waves in Lead II.  | Diabetes mellitus. Moderate anemia. The precordial pain was not anginal in type.        |
| 58                                 | Complaint of dyspnea on exertion. Extrasystoles.   | Has been under observation two years.   | 60   | History not obtainable. T-waves low in all leads. Extrasystoles. Orthodiagram shows slightly enlarged heart.  |   |
| 32                                 | A physician apprehensive about extrasystoles. No other symptoms; no positive physical signs except extrasystoles. Small T-wave in Lead II. Heart transversely placed but of normal size. | Has had extrasystoles since he was a medical student eight years ago. The small T-2 was regarded as due, in all probability to the position of the heart. | 43   | Tachycardia observed during convalescence from alcoholic bout. No other cardiovascular findings.  | Died shortly after this study was made in another bout of alcoholism.                   |
| 59                                 | No cardiovascular symptoms. No positive physical findings.   | Renal glycosuria. Has been under observation of various physicians for many years.  | 38   | Obesity; palpitation, precordial discomfort, dyspnea on exertion. X-ray picture shows slight generalized enlargement of heart. Low T-wave in Lead II. | Highly neurotic, although findings suggest cardiovascular disease.                      |
| 41                                 | Numerous and varied complaints, including precordial pain, radiating down left arm. No positive physical findings except obesity.  | Complete studies made in medical ward.  | 40   | History of dyspnea on exertion, weakness, dizziness, swelling of ankles. These came on in association with attack of arthritis.                       | Negative on reexamination, but electrocardiogram no longer showed significant Q-3 wave. |
|                                    |  |   | 27   | History of precordial pain, palpitation, dyspnea, edema of ankles. No positive physical findings.   |   |
|                                    |  |   | 44   | Tachycardia and slight cyanosis.  | Negative on reexamination but electrocardiogram no longer showed significant Q-3 wave.  |

The diagnosis of the twelve cases in the groups considered negative or doubtful were as follows: extrasystoles only—4, cardiac neurosis—2, diabetes mellitus—1, alcoholism—1, renal glycosuria—1, undiagnosed—3.

The data of possible significance from the cardiovascular viewpoint is listed in Table II. These cases presented diagnostic difficulties and the classification is arbitrary. Cases were classed as negative when none of the available evidence seemed to point to cardiovascular disease. There were five cases in this group. Of these, three were elderly (fifty-eight, fifty-nine and seventy-three years of age). The possibility must be conceded that cardiac damage, which we were unable to detect, was present. The other two patients were forty-one and twenty-six years of age; the former was obese, the latter had a transversely placed heart and his electrocardiogram showed numerous extrasystoles.

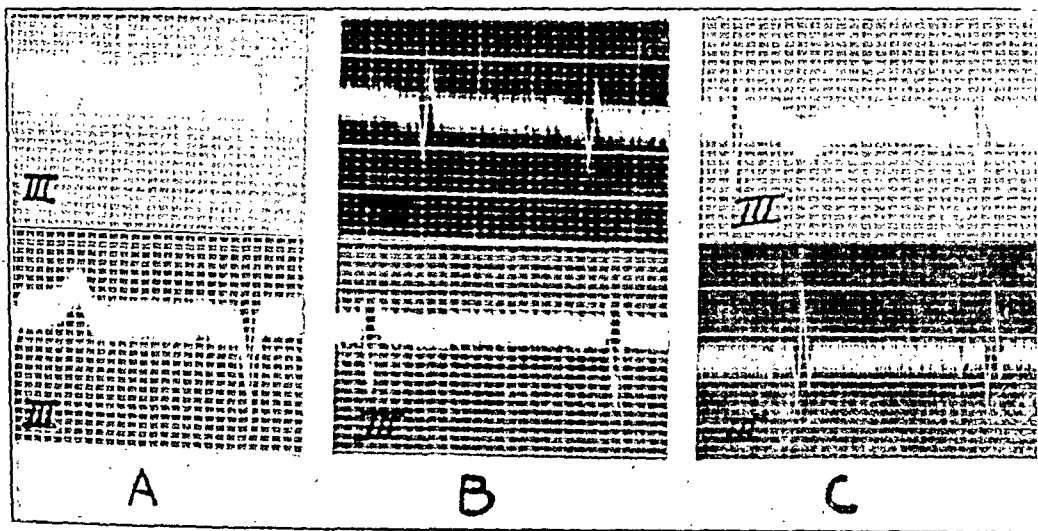


Fig. 1.—Variability of significant Q-3 waves. In each case a period of several months elapsed between the first and second tracings. A and B are from cases with the anginal syndrome; C (upper tracing) is from a pregnant woman; the lower tracing was taken several months after delivery.

Seven cases were classified as doubtful because their complaints or findings pointed to cardiac damage but sufficient evidence was not found to warrant a definite diagnosis.

In this entire group of 78 cases with significant Q-3 waves the electrocardiograms were otherwise normal in 38 cases; there were T-wave changes in 32; the QRS complexes were slurred in four; and four cases showed various degrees of heart-block.

*Group IV.*—The electrocardiograms of one hundred and sixteen cases with the anginal syndrome (angina pectoris or coronary occlusion or both) were examined. There were 31 cases with significant Q-3 waves (26.7 per cent). The majority (62 per cent of the entire group) showed a left axis deviation, the QRS complex of Lead III in many showing (1) a small upright wave followed by a deeply inverted wave and occasionally by another upright wave; (2) a single inverted wave; or (3) an in-

verted wave followed by an upright wave. Tracings repeated later in some of these patients showed changes in the QRS complexes, which although slight, were sufficient according to Pardee's criteria, to compel a reclassification. Some developed significant Q-3 waves and others lost them (Fig. 1, *A* and *B*).

Among the 31 cases with significant Q-3 waves, the electrocardiograms were normal in other respects in eight cases; T-wave changes were present in 22 cases. One showed numerous ventricular extrasystoles.

*Group V.*—The electrocardiograms of 145 corporation executives were studied. This material was obtained from a health survey made by Dr. T. Grier Miller and one of us (C. C. W.). The cases studied comprised practically all of the executives stationed in a single geographic unit of one corporation. The data were considered to have some value as a control particularly for Group IV. None of these corporation executives appeared to be suffering from the anginal syndrome (although one has since developed coronary occlusion); nevertheless their age incidence was comparable to that of sufferers from the anginal syndrome. Furthermore, they represent a class from which many victims of angina pectoris are recruited, namely business men carrying heavy responsibilities.

There were eight significant Q-3 waves in this group. The clinical and fluoroscopic data of the eight cases were then studied and seven showed evidence of heart disease. In the eighth individual, a man forty-seven years of age, repeated studies over the course of three years have failed to reveal any evidence of cardiovascular disease.

The electrocardiograms showing a significant Q-3 wave were otherwise normal in three cases; two showed T-wave changes and three other abnormalities.

*Group VI.*—In order to determine whether a high diaphragm favors the production of a significant Q-3 wave, electrocardiograms of twenty-five pregnant women (ninth month) were made. In evaluating the findings in this group, cognizance must be taken of the fact that other factors besides elevation of the diaphragm influence the heart during pregnancy.

There were four deep Q-3 waves but only 3 (12 per cent) were considered significant. The fourth was found in a tracing which also showed a right axis deviation.

Several months after delivery, electrocardiograms were repeated on two of the three patients; in both instances there was a disappearance of the significant Q-3 wave (Fig. 1, *C*).

#### DISCUSSION

*Clinical Importance.*—The finding of but one significant Q-3 wave among the electrocardiograms of 826 college students with presumably normal cardiovascular systems reflects the rarity of this wave in the tracings of healthy adolescents and young adults. Furthermore, the



fact that this one significant Q-3 wave led to the discovery that its possessor had frank valvular disease, and that his record had been improperly filed offers an illustration of the fact that this finding must not be passed over too readily. Pardee found two significant Q-3 waves in 227 records from presumably normal individuals. In both of these the position of the heart was more horizontal than the average.

The inclination of the heart in the body has been shown to influence the form of the electrocardiogram. In cases with high position of the diaphragm, significant Q-3 waves appear to be found more often than in controls. The disappearance of a significant Q-3 wave following delivery in two of our cases suggests that a change in position of the heart, as a result of an elevated diaphragm, had probably been responsible for the production of this wave. However, other conditions influence the heart during pregnancy and may possibly be factors in the production of this wave.

The percentage (6 per cent) of significant Q-3 waves found in 500 ward and clinic cardiovascular cases corresponds closely to the figure (7 per cent) obtained by Pardee in a study of 200 private cases. Willius,<sup>5</sup> however, found but 300 significant Q-3 waves in 70,000 electrocardiograms (0.04 per cent). The differences of incidence doubtless depend mainly on the type of material studied (Table III). Sixty-three

TABLE III

|  | TOTAL NUMBER<br>WITH SIGNIFI-<br>CANT Q <sub>3</sub> WAVES | ANGINAL<br>SYNDROME | HYPERTENSION<br>AND/OR ARTERIO-<br>SCLEROSIS WITH-<br>OUT THE ANGI-<br>NAL SYNDROME | SYPHILITIC<br>CARDIO-<br>VASCULAR<br>DISEASE | RHEU-<br>MATIC<br>TYPE<br>HEART<br>DISEASE |
|--|--|---------------------|---|--|--|
| Pardee (number<br>of cases not<br>stated)                                  | 43   | 27 (63%)            | 2 (4.6%)  | 1 (2.32%)                                    | 4 (9.3%)                                   |
| Edeiken and<br>Wolferth; 500<br>ward and clinic<br>cardiovascular<br>cases | 31   | 5 (16%)             | 10 (33%)  | 8 (25.8%)                                    | 3 (9.7%)                                   |
| Willius, 70,000<br>electrocardio-<br>grams                                 | 300  | 115 (38.3%)         | 153 (51%)   | 7 (2.3%)                                     | 8 (2.7%)                                   |

per cent of the significant Q-3 waves in Pardee's group were found in patients suffering from the anginal syndrome, whereas the incidence was only 16 per cent in the 500 ward and clinic cases in this study. Willius found 38.3 per cent of all significant Q-3 waves in electrocardiograms of patients with the anginal syndrome. The percentage of deep Q-3 waves found in other heart conditions also varies in different studies (Table III).

In our series of cardiovascular cases, more Q-3 waves were discovered in patients with hypertensive cardiovascular disease (with no anginal

history) than in cases with the anginal syndrome (whether hypertensive or not). It is noteworthy that 8 of the 31 significant Q-3 waves in the group of 500 ward and clinic cardiovascular cases occurred in syphilitic cardiovascular disease. Although the number of cases is small, it would appear that the relationship cannot be regarded as accidental.

The incidence of Q-3 waves found in 1900 consecutive electrocardiograms (4.2 per cent) is, as might be expected, lower than that obtained in the five hundred ward and clinic cardiovascular cases (6 per cent).

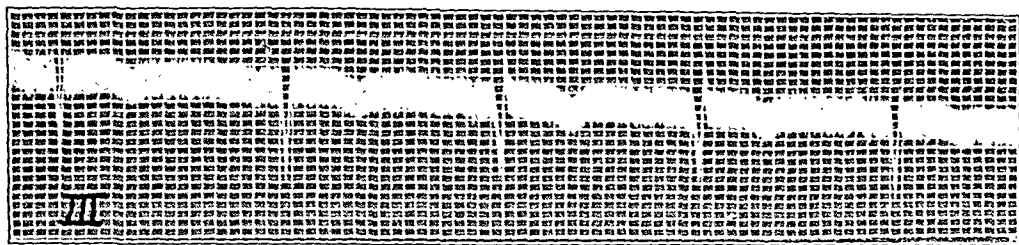


Fig. 2.—Variability of Q-3 wave in successive beats; respiration was not deep.

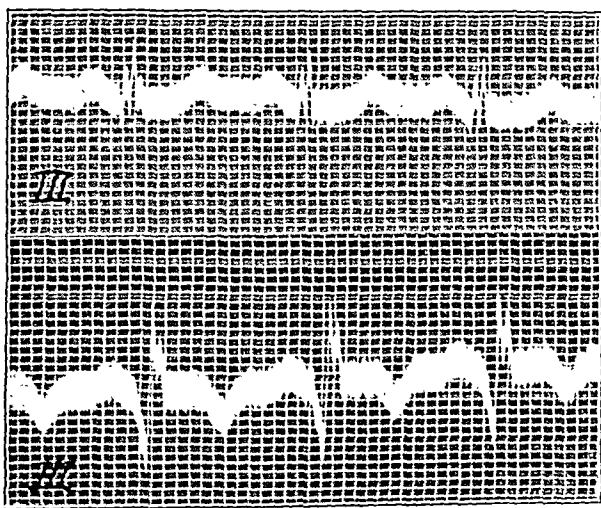


Fig. 3.—Lead III before and following coronary occlusion. Appearance of a significant Q-3 following occlusion. Interval between tracings was three and one-half months.

Among these 1900 there were many tracings made as part of a routine examination in patients who neither complained of cardiac symptoms nor showed evidence of cardiac disease on physical examination.

The high percentage (26.7 per cent) of significant Q-3 waves in the electrocardiograms of patients suffering from the anginal syndrome confirms the observation of Pardee that these patients show the deep Q-3 more often than cardiac patients in general. In Pardee's group of 200 unselected cardiacs, there were 30 cases of angina and 8, or 27 per cent, of these showed a significant Q-3. This incidence is almost identical with that of our group of 116 cases with the anginal syndrome.

Although a Q-3 wave was seen in 26.7 per cent of patients with the anginal syndrome and about 6 per cent of all cardiacs studied, the prob-

ability exists that it occurs in a much larger percentage of cases at one time or other. We have pointed out above that some of our cases of angina pectoris showed a significant Q-3 wave on one examination and failed to show one on another occasion (Fig. 1, *A* and *B*). As a matter of fact a single strip of tracing may show this variation (Fig. 2). Furthermore, the Q-wave may disappear during an attack of angina pectoris as shown in a record published by Wood, Wolferth and Livezey<sup>6</sup> (Fig. 5 of their paper).

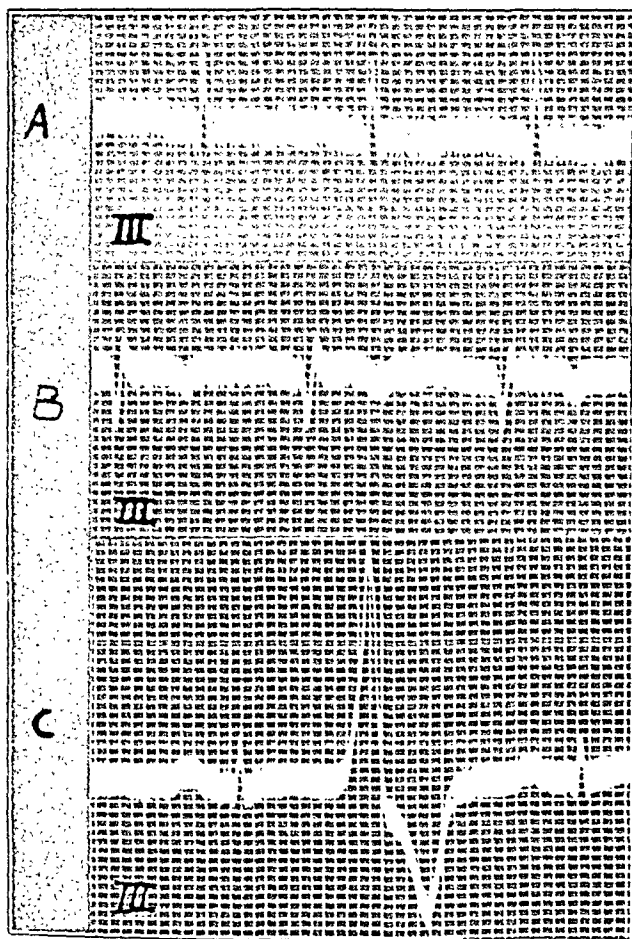


Fig. 4.—Lead III from patient with rheumatic heart disease. The three tracings were made over a period of one year; only one (*B*) showed a significant Q-3 wave.

Parkinson and Bedford<sup>2</sup> have noted the Q-wave in Lead III in some of their cases of coronary occlusion (9 times in 28 published cases). Fenichel and Kugell<sup>7</sup> have demonstrated the marked frequency of this wave in cases of occlusion with septal involvement. The possibility must be conceded, however, that the Q-wave might have been present in some of these cases prior to the occlusion. In Fig. 3 is shown one of three instances which we have seen of the development of a Q-3 wave (after a coronary occlusion) which had not been present prior to the occlusion.

The variability in the Q-3 wave is also observed in cases of rheumatic heart disease. In the electrocardiogram of a young man with rheumatic

mitral stenosis, during an attack of paroxysmal auricular tachycardia, a right axis deviation and a deep Q-3 wave were observed. Eight days later and five days after the cessation of the tachycardia under quinidine therapy, the right axis deviation and Q-3 were no longer present. In another case of rheumatic mitral stenosis (Fig. 4) only one of three tracings taken over a period of one year showed a deep Q-3 wave. In another case (Fig. 5) a significant Q-3 wave appeared only after an extrasystole.

The corporation executives used as a control, particularly for the anginal group, cannot be considered as an entirely normal group for some had demonstrable cardiac damage. The Q-3 wave was found in eight instances, and in seven of these there was definite evidence of

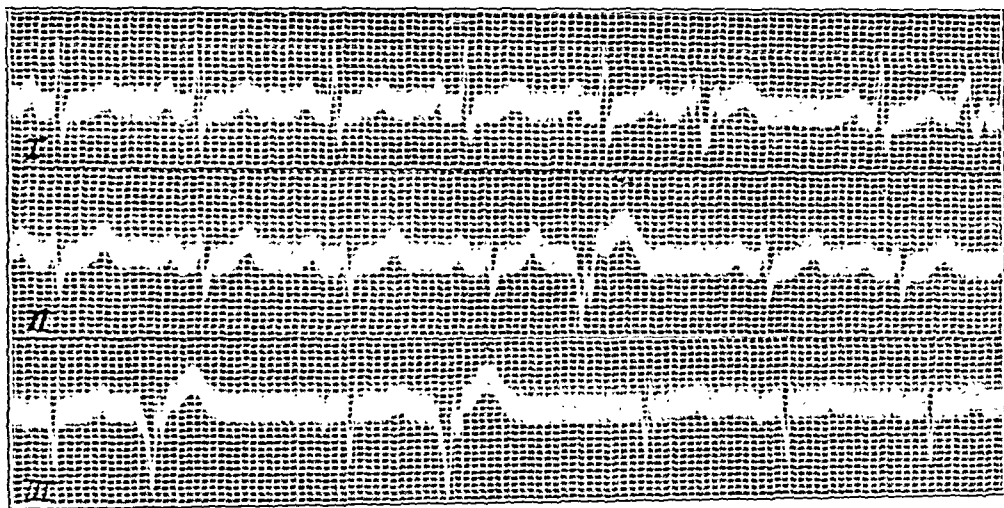


Fig. 5.—Electrocardiogram of a patient with rheumatic heart disease. A significant Q-3 wave appears after an extrasystole.

cardiac damage, although none complained of cardiovascular symptoms. Thus it would appear that the Q-3 wave is not only a fairly frequent finding in hypertensive or arteriosclerotic heart disease not sufficiently advanced to cause symptoms, but that when present it has considerable diagnostic value.

#### MECHANISM

It is generally believed that the interventricular septum is concerned in the production of the Q-wave. According to Lewis,<sup>8</sup> activation of the septum is responsible for the Q-wave and the beginning of the R-wave in all leads. It would seem, therefore, that increase in amplitude of the Q-wave beyond what is usually seen must be related to the spread of the excitatory process throughout the septum. On this basis, several possibilities that might account for a deep Q-3 wave suggest themselves: (1) The septum may be involved by a lesion which disturbs the spread of the excitatory process; (2) the septum may be increased in size; (3) the septum may be normal except for eccentricities in the distribution of the

conduction pathways; (4) the septum may be deviated from its usual position with reference to Lead III.

1. Fenichel and Kugell<sup>7</sup> found at necropsy a high incidence of involvement of the posterior part of the septum in the cases of coronary occlusion whose electrocardiograms exhibited a deep Q-3 wave. All of their 17 cases with large Q-3 revealed septal involvement at least in the posterior part. In the 16 cases without a large Q-3 only one showed involvement of the posterior portion of the septum. In material such as we report, however, it seems improbable that infarction of the septum, or other damage severe enough to modify the course of the excitatory process materially was present in more than a small minority of cases.

2. The suggestion that enlargement of the septum may be responsible for a deep Q-3 wave must remain for the present, at least, purely a speculation. The only point which we can make in support of this suggestion is the comparative frequency of deep Q-3 waves in subjects with hypertensive cardiovascular disease and enlarged hearts. On the other hand, the great majority of patients with marked enlargement of the heart and presumably some enlargement of the septum fail to show a deep Q-3 wave. Furthermore, many of the patients whose electrocardiograms exhibit a deep Q-3 wave, have no appreciable cardiac enlargement. Thus it seems unlikely that enlargement of the septum is a factor of major importance in accounting for the clinical incidence of the deep Q-3 wave.

3. Anomaly of pathways of conduction (aside from actual defect in conduction) is purely a theoretical conception that has been utilized previously, especially in the attempt to account for axis deviation in the absence of cardiac enlargement or displacement. Such a mechanism, as Pardee suggested, may be thought of as a possible explanation of the deep Q-3 wave in cases with normally placed hearts which show neither evidence of enlargement nor other pathological changes. The rarity of significant Q-3 waves in healthy young individuals, however, indicates that such an hypothesis has little if any practical application.

4. A factor which we believe deserves serious consideration, as a major cause of deep Q-3 waves, is change in position of the septum with reference to the plane of Lead III. There is considerable evidence to support such a view. The fact that on change in position one wave of the QRS complex may show marked changes without proportionate changes in other waves was demonstrated by Einthoven and deLint.<sup>9</sup> They showed that if an electrocardiogram was made with the subject lying on the left side and the procedure repeated with the subject on the right side, the S-wave, in Lead I of the second tracing tended to be deeper than in the first, although there was usually no material change in the R-wave.

In experiments on dogs, Meek and Wilson<sup>10</sup> demonstrated the marked influence of rotation of the heart on the QRS complexes of the electrocardiogram. According to these authors, either uncomplicated rotation of the apex to the right on the anteroposterior axis or rotation on the

longitudinal axis turning the front of the heart toward the left will give curves characteristic of right-sided preponderance. The opposite movements will give curves characteristic of left-sided preponderance. Mere displacement of the heart to the right or left usually causes a combined rotation on both anteroposterior and longitudinal axes and produces electrocardiographic changes which cannot be predicted because of the opposing effects of simultaneous rotation around the anteroposterior and longitudinal axis. For example, pulling the heart to the left produced left axis deviation in the majority of cases but also caused an increased incidence of Q-3 from 45 to 68 per cent in 30 experiments. Q-3 is frequently seen in electrocardiograms with right axis deviation and is seldom found in left axis deviation. Pulling the heart to the right side did not produce a right axis deviation; Q-1 either appeared or, if already present, increased in 26 of 29 cases (90 per cent) and Q-3 was found in

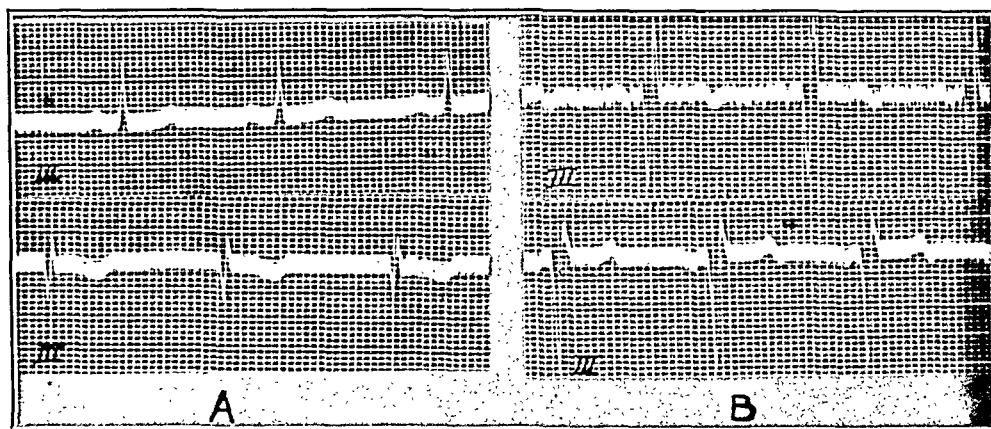


Fig. 6.—A, Production of a deep Q-wave by transferring the left leg electrode to the region of angle of left scapula (lower tracing). Upper tracing shows Lead III taken in conventional manner. B, A significant Q-3 wave made deeper by the above procedure.

only 34 per cent of all records, a decrease of 11 per cent from normal. This is not what was expected, since Q-1 is seldom found in right axis deviation. However, by limiting the movement of the heart to rotation around its longitudinal axis or by pulling the heart to the left or right and then correcting for the longitudinal rotation, they could produce tracings typical of left and right axis deviation.

The observations of Meek and Wilson, therefore, have a bearing on (a) the varied effects on the electrocardiogram produced by attempts at rotation of the heart in the human, and (b) the findings of a deep Q-3 wave in electrocardiograms with left axis deviation. We attempted to produce a significant Q-3 wave in subjects with presumably normal hearts by taking tracings with the body in various positions. Although marked changes in QRS complexes were produced by changes in position of the body and presumably of the heart, Q-3 was not produced. However, by rotating the plane of the lead in relation to the heart, the electrodes can

be so placed that a Q-wave is produced. This can be done by leaving the left arm electrode in position and transferring the left leg electrode to the region of the angle of the left scapula (Fig. 6, A). By the same type of procedure a Q-wave already present can sometimes be made proportionately deeper (Fig. 6, B). In certain cases, however, Lead III taken with the patient in the upright position may be the most favorable procedure for recording the Q-wave. Thus in one patient with aortic insufficiency and mitral stenosis, the electrocardiogram with the patient in

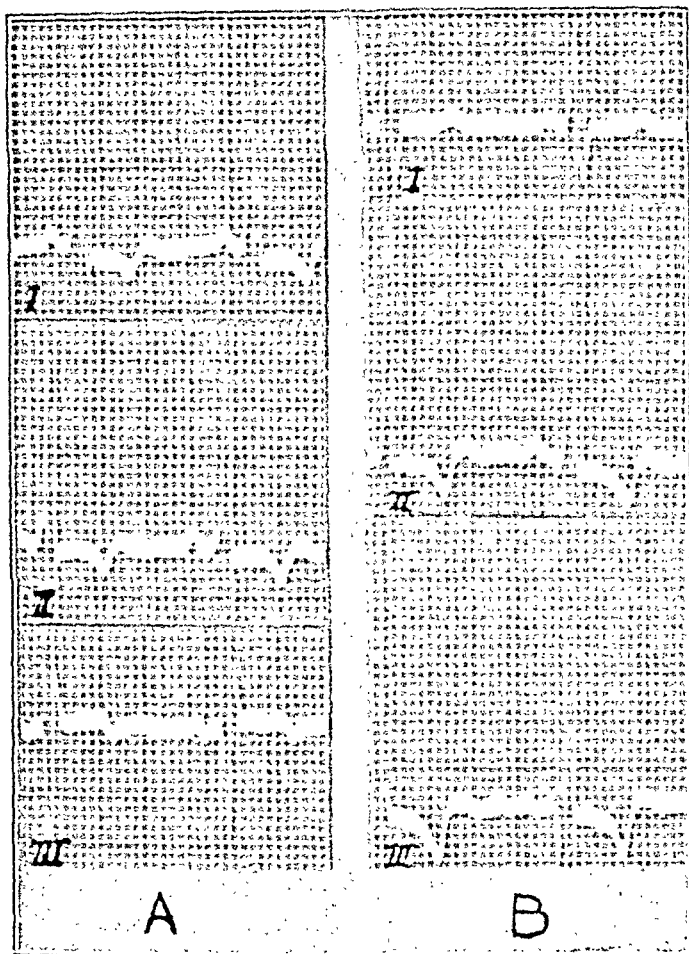


Fig. 7.—Records showing effect of position of body upon a deep Q-3 wave. A, Patient in sitting position. B, Tracing taken immediately after A, with patient on left side.

the upright position showed left axis deviation and a deep Q-3. By changing the position of the patient, it was possible to produce right axis deviation and at the same time diminution of the Q-3 wave (Fig. 7).

From the above considerations, it would appear that not only may rotation of the septum determine the presence or absence of a deep Q-3 wave but the degree of rotation need not be great. The factors which determine such rotation in human hearts are not well understood and must be studied further if the mechanism of the deep Q-3 wave is to be worked out. For the present we must content ourselves by calling at-

tention to the importance of the position of the septum with reference to the plane of the electrocardiographic lead. The reasons why a deep Q-3 wave in association with a normal electrical axis or deviation to the left occurs in a certain proportion of cases with evidences of myocardial damage and is rare in cases with presumably healthy hearts remain obscure.

#### SUMMARY

1. In the electrocardiograms of 709 apparently normal college students, no significant Q-3 waves were discovered. Among 117 college athletes, the only significant Q-3 wave occurred in an individual with rheumatic heart disease.

2. A significant Q-3 wave was found in approximately 6 per cent of 500 hospital, ward and clinic patients with cardiovascular disease. Although all ages were included, the youngest patient to show a significant Q-3 wave was thirty-two years of age; the oldest was seventy-two years. Hypertension, arteriosclerosis and syphilis were regarded as the etiological factors of the heart disease in the majority of cases, but significant Q-3 waves were also seen in cases of rheumatic and thyrotoxic heart disease.

3. In nineteen hundred unselected electrocardiograms taken from the files of the Cardiographic Laboratory, including ward, clinic and private patients of all ages, there were 78 (4.1 per cent) significant Q-3 waves. Of the 78 individuals exhibiting the significant Q-3 waves, 63 were classified as having heart disease, 7 were placed in a doubtful group, 5 were considered negative, and 3 were not classified because of inadequate records.

4. Thirty-one or 26.7 per cent of one hundred and sixteen cases of the anginal syndrome showed a significant Q-3 wave.

5. Eight or 5.5 per cent of the electrocardiograms of one hundred and forty-five corporation executives showed a significant Q-3 wave. In seven of these eight cases there was definite evidence of cardiovascular disease, although the history in all was negative.

6. A total of 149 significant Q-3 waves was found in the first five groups of this study. The electrocardiogram was otherwise normal in 68 cases; 64 showed T-wave changes; and 17 other electrocardiographic abnormalities. This sign, therefore, may constitute the first electrocardiographic change to invite attention to the possibility of cardiac damage.

7. Twenty-five pregnant women in the ninth month, were electrocardiographed, and three were found to show significant Q-3 waves. In two of these who were reexamined, several months after delivery, the Q-3 wave had vanished.

8. Available evidence indicates that the conditions chiefly responsible for deep Q-3 waves are either (1) a lesion of the septum which interferes with the spread of the excitatory process, or (2) deviation of the septum



from its usual position with reference to Lead III of the electrocardiogram.

9. Study of the clinical incidence of the deep Q-3 wave suggests that in the majority of cases change of position rather than injury severe enough to alter the spread of the excitatory process, is the important factor in the production of this wave.

10. Deep Q-3 waves which conform to the criteria of Pardee are occasionally present in electrocardiograms of patients who show neither evidence of cardiac disease nor changes from the normal in the size and position of the heart. Whether or not this is due to some peculiarity in the ventricular tissues first invaded by the excitatory process, cannot be stated. It is important, however, to take these cases into account when the attempt is made to evaluate the clinical significance of the deep Q-3 wave.

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# HEART DISEASE IN THE AMERICAN NEGRO OF THE SOUTH\*

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A RECENTLY reported investigation<sup>1</sup> disclosing the greater prevalence of organic heart disease in the negro as compared with the white race makes pertinent an examination into the incidence and course of this group of diseases in the black race, a subject heretofore inadequately considered.<sup>2, 3, 4</sup>

Among 10,188 new patients (4,252 white and 5,936 negro patients) seen in the Medical Division of the Dispensary of the John Sealy Hospital during the past seven and one-half years, there were found 1,660 cases of organic heart disease. This group comprised 488 white patients and 1,172 negro patients, which makes the incidence of organic heart disease in medical patients for the two races 11.5 and 19.7 per cent, respectively. It follows from this analysis that in the medical patients seen in this Dispensary organic heart disease of all varieties occurs one and seven-tenths times more often in the negro than in the white race.

The average age of the negroes with all types of organic heart disease was found to be 46.6 years, whereas the average age of the white patients in the series was 56.3 years. Manifestly, organic heart disease of all varieties occurs on the average 9.7 years earlier in the life of the negro than in the white patient.

That the mortality rate from heart disease in the negro is higher than that in the white race is a well established fact. Dublin,<sup>5</sup> in studying the death rates from the Industrial Department of the Metropolitan Life Insurance Company, found that negro males show death rates from heart disease, during the main period of life, from 65 to 80 per cent higher than white males of the same ages and for negro women the rates are twice as high as for white women of similar age periods. Corroborative of these facts is the report of Woody<sup>6</sup> who, in a study of death rate statistics in the southern states, arrived at similar conclusions. Holt<sup>7</sup> compared the death rates of the white and negro races in Little Rock and Arkansas and found the death rate from heart disease to be 80 per cent higher in the negro than in the white race.

Not only is the mortality rate from heart disease higher in the negro than in the white race, but, likewise, the resulting morbidity is of much greater degree. It has long been a common observation of those who see many negro patients that a diagnosis of organic heart disease in the

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case of a negro is of much more serious import than a similar diagnosis given a white patient. Such, it is offered, would be anticipated in view of the fact that the economic status and mode of living of the negro would prevent him from caring for himself in a manner that the white patient could and would. However, it should be added that the same difficulties are encountered in the treatment of heart disease in any individual, regardless of race, who is dependent upon manual labor for sustenance. The majority of the white patients with whom we have compared the negro in this regard were of practically the same social stratum and worked and lived under similar conditions. Therefore, logical as the explanation cited may at first appear, it fails to reconcile the discrepancy in the mortality and morbidity rates from heart disease in the two races.

#### HYPERTENSIVE CARDIOVASCULAR DISEASE

The prominence of syphilis as a cause of heart disease in the negro is universally appreciated; however, the rôle played by hypertension as a causal agent of heart disease in this race has failed to receive the emphasis which its importance as such a factor warrants.

In our initial investigation previously referred to, it was found that the incidence of hypertensive cardiovascular disease in the patients coming to the Medical Division of the Dispensary was 12.5 per cent for negroes and 4.9 per cent for white patients from which it follows that this type of heart disease in medical patients in this Dispensary is of two and one-half times greater incidence in the negro than in the white race. Analysis of these same data in regard to both race and sex revealed the following incidence figures: negro males 10.6 per cent, white males 3.7 per cent, negro females 14.7 per cent, and white females 6.6 per cent. These figures justify the conclusion that in this clinic this type of heart disease is of three and one-tenth times greater incidence in the negro male than in the white male, and of two and two-tenths times greater incidence in the negro female than in the white female. It is also obvious that hypertensive cardiovascular disease in this clinic occurs one and one-half times more often in the negro female than in the negro male.

A comparison of the age incidence in the negro and in the white patients with this form of heart disease is in point, and the discrepancy in this regard is sufficiently striking to merit a detailed consideration. The average ages for patients with hypertensive heart disease were found to be as follows: white males 54.6 years, white females 51.1 years, negro males 47.7 years, and negro females 43.4 years. The conclusion is therefore justified that in this clinic hypertensive heart disease occurs, on the average, seven years earlier in the life of the negro than in that of the white patient. An analysis of the ages of the patients in regard to the occurrence of hypertension by decades revealed that in white

patients the cases were distributed as follows: 20 to 30 years, 0.5 per cent; 30 to 40 years, 3.4 per cent; 40 to 50 years 30 per cent; 50 to 60 years, 40.4 per cent; 60 to 70 years, 23.1 per cent; 70 to 80 years, 2.5 per cent. These figures are in considerable contrast to those for the negro race which were as follows: 10 to 20 years, 0.13 per cent; 20 to 30 years, 5.5 per cent; 30 to 40 years 25.1 per cent; 40 to 50 years, 34.2 per cent; 50 to 60 years, 26.1 per cent; 60 to 70 years, 8.2 per cent; 70 to 80 years, 0.7 per cent.

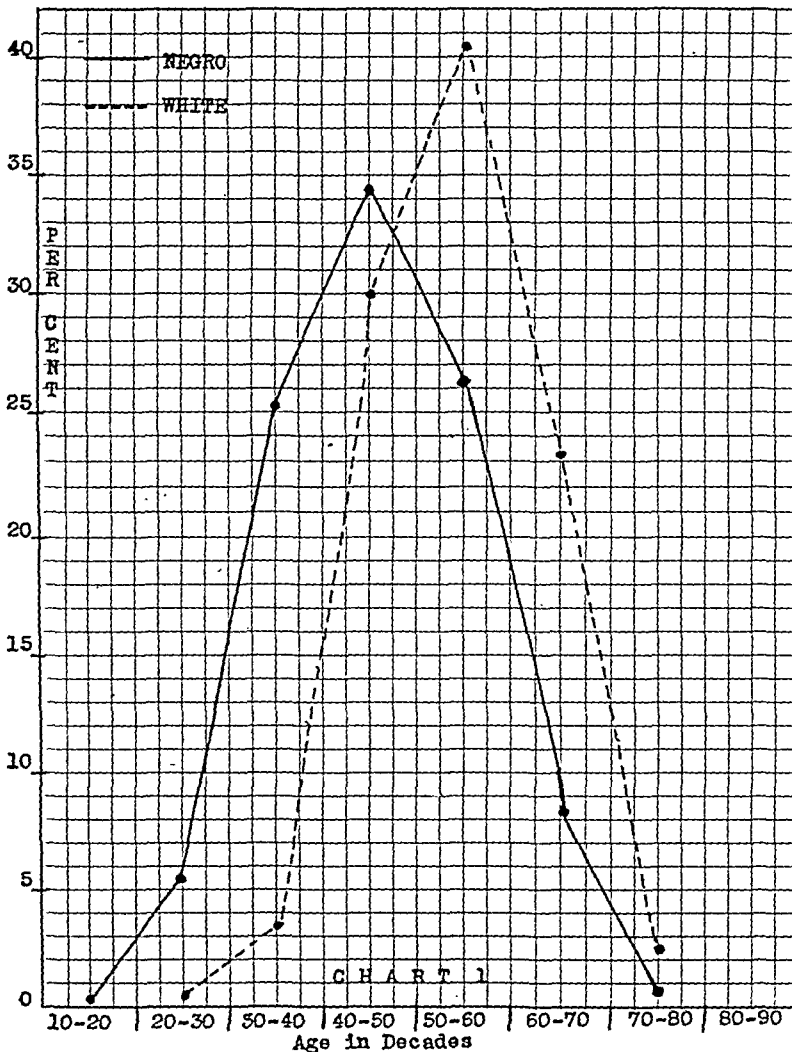


Chart 1.—A comparison of the occurrence by decades of hypertensive cardiovascular disease in the white and negro races.

to 80 years, 0.7 per cent. Thus, it is seen that the greatest incidence of hypertensive heart disease in the negro race occurs in the fourth decade, whereas in the white race the peak is reached in the fifth decade. And it is likewise apparent that 65 per cent of the cases of this type of heart disease in the negro occur prior to the fiftieth year of life, whereas in the white race 65 per cent of the patients had already passed that period in life. The most marked difference in incidence lies in the third

decade at which time vascular hypertension is of nearly eight times greater incidence in the negro than in the white race. The differences in the two races in this regard are depicted graphically in Chart 1. A comparison of data computed in a like manner with reference to the occurrence of hypertension in negro males and females reveals that this condition occurs earlier in the life of the female than in the male. This compilation discloses that approximately 71 per cent of the cases of

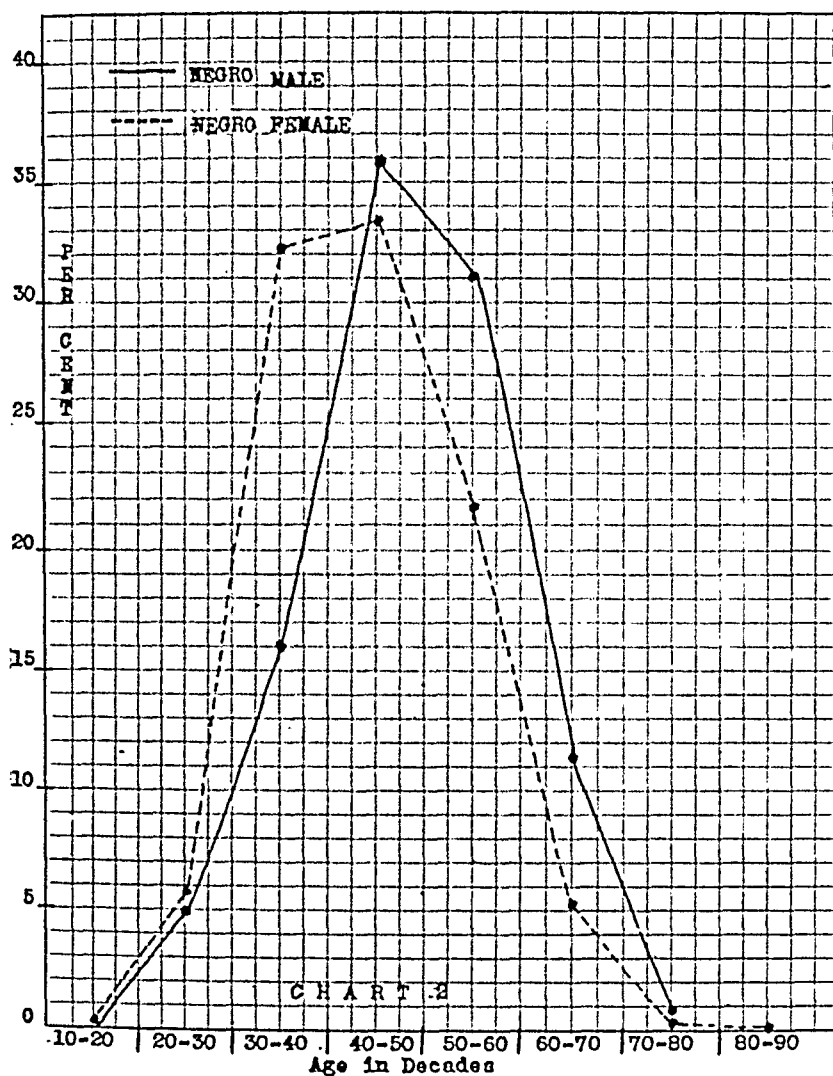


Chart 2.—A comparison of the occurrence by decades of hypertensive cardiovascular disease in negro males and females.

hypertension in the negro female occur prior to the fiftieth year whereas only 57 per cent of the cases in the negro male appear prior to that period in life. Likewise, it is manifest that the incidence in the third decade is twice as great in the female as in the male negro (Chart 2).

Just as there is considerable difference in the two races in regard to the incidence and age of occurrence, so the course of hypertensive cardiovascular disease in the negro is quite unlike that in his white brother. Although our patients were not subclassified into benign, severe benign,

and malignant types as suggested by Keith and his associates,<sup>8</sup> a small experience with negroes who have hypertensive cardiovascular disease is sufficient to impress one with the logic and merits of the use of the term "malignant hypertension," for in the negro and particularly the negro in the third decade of life, the hypertension is frequently of a most fulminating type, death occurring early from what often appears to be a combined insufficiency of the heart, kidneys, and brain. The course of the disease in general is much more rapid, the complications promptly follow recognition of the hypertension, and death occurs much sooner than would ordinarily be anticipated in the white patient with this disease. The inevitable complications of essential hypertension manifest themselves in the negro predominately in the heart and kidneys. Cerebral hemorrhage is a much less frequent cause of death in the negro than in the white race. A study of the causes of death obtained from postmortem examinations in a small series of negroes dying from hypertension and its complications yields results appreciably different from those reported by Bell and Clawson<sup>9</sup> whose series, we assume, includes only white patients. Considerable difficulty was encountered in many instances in determining the true cause of death, as in many cases renal and cardiac factors were inseparable. It should be mentioned that many of the deaths due to uremia were preceded by one or more breaks in compensation. Although the study is not yet complete, it appears that the incidence of myocardial deaths was about the same, renal deaths were about twice as common in the negro, and cerebral deaths, hemorrhage and encephelomalacia, only about one-half as frequent in the negro as in the white race.

#### SYPHILITIC CARDIOVASCULAR DISEASE

In the investigation referred to above,<sup>1</sup> heart disease of this type was found to occur four times more often in the negro than in the white patient, the percentages for the respective races being 3 per cent for the former and 0.7 per cent for the latter. The average age of the negro patient with this type of cardiovascular disability was 40.6 years and for the white patient 45.5 years.

That syphilis is much more prevalent in the negro than in the white race remains an undisputed fact. Nevertheless, we do not believe that the discrepancy in the incidence of syphilis in the two races is sufficient to account for the fact that syphilitic heart disease occurs four times more frequently in the negro race, more particularly when one considers that the members of the two races in this series were essentially of the same social stratum and economic status. Furthermore, in a given number of patients with syphilis equally divided in number as to race, it is our belief that a larger number of negro patients will develop cardiovascular syphilis than will white patients. Stone and Vanzant<sup>2</sup> have offered the opinion that the cardiovascular apparatus of

the negro is more susceptible to syphilitic infection than that of his white brother. The appearance of cardiovascular syphilis at an earlier age in the negro can be explained in part by the earlier sexual maturity of the negro who, consequently, is exposed to venereal infection earlier in life. It is probable that hard manual labor, though it does not enhance the predilection of the spirochete for the cardiovascular system, may be a factor in aggravating the resulting morbid physiology with consequent earlier symptomatic manifestations.

The relative paucity of cases of uncomplicated syphilitic aortitis (14) compared with the number of cases of aortic regurgitation (134) and aneurysm (31) appearing in the series referred to merits consideration. We are convinced that the characteristic clinical picture of syphilitic aortitis with substernal pain and nocturnal attacks of dyspnea occurs very rarely in the negro. Of all patients placed in this category none had classical symptoms, the diagnosis being made from physical findings, roentgenographic, and serological studies.

The statements made concerning the course of heart disease in general in the negro race are particularly true in the case of cardiovascular syphilis. Heart failure of this etiology is the beginning of an end near at hand. The few who survive the first failure make a partial recovery and live the life of cardiac invalids for a few months at the most.

#### ARTERIOSCLEROTIC HEART DISEASE

The remaining important etiological group in this locality, namely, the arteriosclerotic or coronary artery disease group, differs from the two types previously considered in that it was found to be more prevalent in the white race. The incidence for this type in the medical cases reviewed was 2.7 per cent for the negro and 4.1 per cent for white patients. From this analysis the conclusion is permissible that this type of heart disease in this clinic is of one and one-half times greater incidence in the latter than in the former race. It should be remembered in this connection that arterial disease in advanced stages is by no means uncommon in the American negro. The discrepancy in the incidence of this etiological type in the two races is probably accounted for in a large measure by the fact that a greater number of the white race reach that period in life in which degeneration of the vascular tree commonly occurs. This explanation is corroborated by the findings of Holt<sup>7</sup> who showed that the average duration of life in the negro was 8.3 years less than that in the white race. The opinion is offered that in those negroes reaching the sixth and seventh decades, the incidence of the arteriosclerotic type of heart disease would be greater than that in the white race. This type of heart disease was found to occur, on the average, nine years earlier in the life of the negro than in the white patient. This fact is perhaps very significant in that it strongly suggests an inherent inferiority of the cardiovascular system of the negro.

## ANGINA PECTORIS

In the 10,188 medical cases studied, only eleven cases of angina pectoris were found. The low incidence for this community is in accord with the findings of other observers<sup>2, 4</sup> in the South, and is in contrast to the observations made by investigators<sup>10, 11</sup> in the North and East where angina pectoris appears to be much more common. A more relevant revelation is the fact that all of the 11 cases occurred in white patients; in the 5,936 negro medical patients examined, the syndrome of angina pectoris failed to be discerned in a single instance. This discrepancy in the occurrence of angina pectoris in the two races is difficult to explain, particularly because of the inadequacy of our knowledge concerning the pathogenesis of this symptom complex. We can be almost certain that the cause for this difference does not lie in a dissimilarity of the pathological and functional changes to which the cardiovascular systems of the two races are subjected for the reason that these morbid processes are seen to occur more frequently and to be of a severer degree in the negro than in the white race. The possibility of there being an inherent anatomical difference in the innervation of the heart and great vessels in the two races is so remote that it commands no consideration. Roberts<sup>12</sup> feels that the absence of angina pectoris in the negro is to be accounted for by the fact that nervous and mental strain does not enter into the life of the negro, whereas it is a potent factor in the white races of Western Europe and North America. Certainly, there is a profound dissimilarity in the psyche and sensorium in the two races under consideration. Therefore, it seems logical to assume that the basis for the discrepancy in the occurrence of this syndrome lies in an inherent difference in the sensitivity of the nervous systems in the two races.

## OTHER TYPES OF HEART DISEASE

Unfortunately, the paucity of material representative of the rheumatic and thyrotoxic types of heart disease in the series studied does not permit consideration sufficiently satisfactory to merit the drawing of conclusions. The incidence of these types of heart disease in the group investigated was practically the same for the two races despite the fact that rheumatic fever and hyperthyroidism are appreciably more prevalent in the white race.

## SUMMARY

In view of the facts that heart disease in the negro as compared with the white race is of greater incidence, occurs at a younger age, pursues a more rapid course, and has a higher mortality rate, the opinion is offered that the cardiovascular system of the American negro of the South is inferior to that of the white race, and is more vulnerable to insult whether this be applied as an infection, a degeneration, a toxemia, or in



the form of the stress and strain incident to the complexities and modes of modern occidental civilization.

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# THE ELECTROCARDIOGRAM IN LATE MIDDLE LIFE\*

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## INTRODUCTION

**E**LECTROCARDIOGRAPHIC diagnosis is increasingly concerned with the early recognition of degenerative heart disease occurring in late middle life, and minor changes are often emphasized as indicative of early myocardial damage. Since ordinarily the tests are made because of complaints referable to the cardiovascular system, curves representing the normal heart for this age of life have not been extensively studied. Such series of healthy young adults as have been obtained by Lewis and Gilder,<sup>1</sup> Cohn,<sup>2</sup> and Ferguson and O'Connell,<sup>3</sup> have not dealt with the normal heart in persons over fifty years of age. The purpose of this study was to contribute to the recognition of the normal electrocardiogram for this age and to determine if there are in elderly persons any changes which, though not common in the normal tracings of younger people, must nevertheless be considered physiologic at this stage of life.

## PROCEDURE

Fifty persons between the ages of fifty and sixty-five were selected. They had been admitted to the Barnes Hospital or the Washington University Clinics for a variety of complaints none of which were thought to implicate the cardiovascular system. The patients were excluded if they suffered from marked debility or from an illness which was considered very serious. All of the patients were carefully questioned and denied the presence of symptoms of cardiac disease. They denied all history of heart trouble or of rheumatic fever. On physical examination there were no abnormal findings in the heart. The blood vessels were considered normal for their ages. Specifically, there were no murmurs, demonstrable enlargement of the heart, cardiac irregularities except occasional extrasystoles, and no blood pressures were found to exceed 150 mm. systolic or 90 diastolic. In 43 cases six-foot x-ray plates were taken and the heart measurements were within normal limits. The Wassermann reaction was negative in all cases.

The electrocardiograms were taken with the patients in two positions, sitting (Position 1) and supine (Position 2). A Hindle machine was used in both positions and in addition, for a comparison between the two technics, a Victor machine was employed for the supine position only.

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## FINDINGS

**P-Waves.**—In Lead I the P-waves were upright and normal in 36 cases. In 10 cases they were indeterminate while they were upright in the other leads; in 3 cases they were indeterminate in Leads I and III. They were, in one case, indeterminate in Leads I and II. In no case were they inverted, so it was concluded that the P-waves in Lead I showed very little variation from normal, and then merely a tendency to become iso-electric.

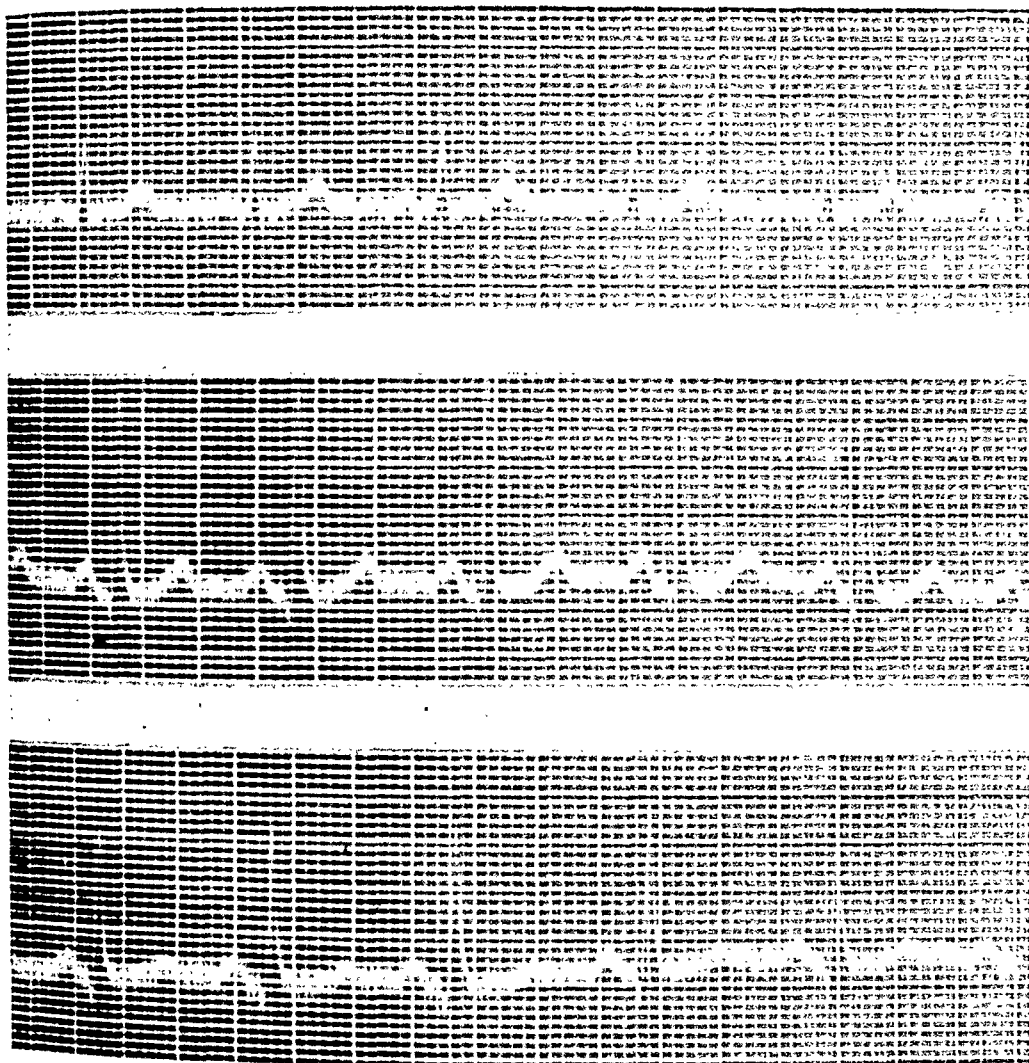


Fig. 1.—Case No. 58, Position 1, showing definite Q-waves in Leads II and III.

In Lead II the P-waves were uniformly high and normal in 49 cases. In 3 of these they changed with position, being higher in Position 1. They were almost iso-electric in one case and had a downward phase in one case. It was concluded that the P-wave in Lead II showed remarkably little variation from the accepted normal and then merely a change with change in position.

In Lead III the P-waves were normal and upright and did not change with position in 31 cases. They were indeterminate in 13 cases; in one

of these they were indeterminate in Position 1, but upright in Position 2, in 2 they were indeterminate in Position 2, but upright in Position 1. The P-waves were inverted in 4 cases and in all of these they became upright on deep inspiration. In one case the P-waves were higher in Position 2 than in Position 1 and in one case higher in Position 1 than in Position 2.

Considering all three leads together it has been found that in 17 cases the P-waves were upright, normal in shape, and not affected by position or respiration. Altogether they showed no difference from what may be expected at any age.

*QRS Complexes.*—In Lead I the complexes consisted of an R-wave only in 21 cases; in 7 there was a definite Q-wave; in 2 of these it was associated with slurring of the downstroke of the R-wave; in one the

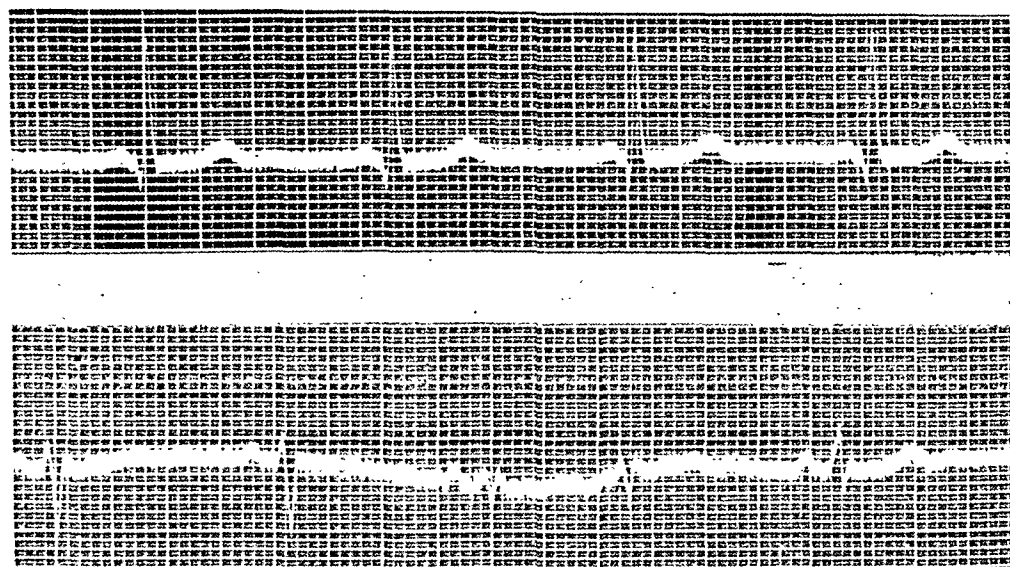


Fig. 2.—Case No. 7, Position 1, Leads I and III showing definite Q-waves in Lead I and transverse heart in Lead III.

R-wave was unusually high and sharp and in one both Q-wave and S-wave were definite.

In 4 cases the S-wave was very deep in both positions; in 3 other cases it was marked in one position only, in 2 cases more marked in Position 1 than in Position 2, in 1 more marked in Position 2 than in Position 1. In 1 case only was it sufficiently marked to constitute right axis deviation.

Slurring of the upstroke of the R-wave occurred in 2 cases, and of the downstroke in 8 cases; in 1 of these it was interpreted as high branching. In 5 cases there was slight slurring of the entire complexes. In one case the voltage was very high and in another very low.

In Lead II the Q-waves were marked in 3 cases, in 1 case more in Position 1 than in Position 2. In 1 case the Q-wave was accompanied by a slurring of the descending R-wave.

The descending limb of the R-wave was slurred in 6 cases; 2 of these

also showed "high branching"; 1 showed a notch like an S-wave during the downstroke. Slurring of the ascending R occurred in 3 cases, in 1 both upstrokes and downstrokes were slurred. In 13 cases there was an R-wave only.

The S-wave was marked in 18 cases, in 1 more so in Position 1 and in 2 more so in Position 2. In 3 of the 18 cases the S-waves were both wide and slurred.

The entire QRS complex in Lead II was slurred in 5 cases; in 1 of these the slurring was more marked in Position 1. In 2 cases the complexes were low, in 1 of these it was more pronounced in Position 2.

In Lead III the Q-wave was absent in 35 cases, its presence was doubtful in 5 cases, in 10 it was present and well defined, in 4 of these it exceeded 25 per cent of the greatest excursion of the QRS complex, thus

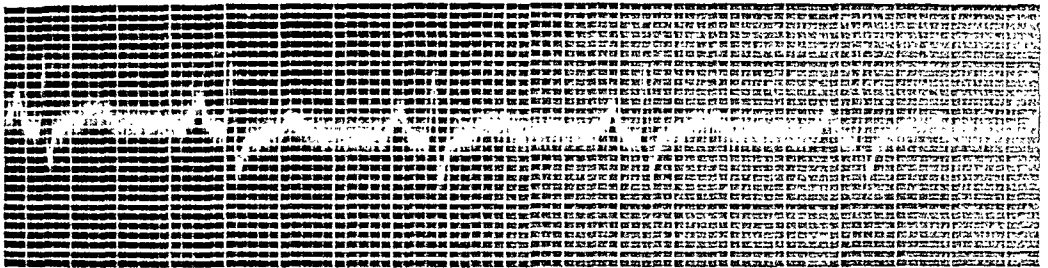


Fig. 3.—Case 43, Position 1, Lead II showing marked slurring and widening of S-wave.

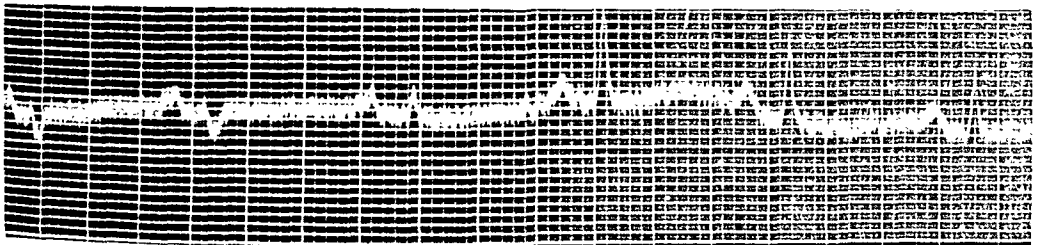


Fig. 4.—Case 45, Position 1, Lead III showing small slurred complexes becoming sharp and upright on deep inspiration.

complying with Pardee's criterion.<sup>4</sup> In 3 cases there was an inverted complex and it could not be determined with certainty whether this was a Q, an S, or an inverted R-wave. Change in position caused the Q-wave to change in 7 cases, in 2 it was deeper in Position 2 than in Position 1, in 5 it was more marked in Position 1 than in Position 2.

The R-wave was slurred in 48 cases and in 35 of these it was also low, in the other 13 it was of moderate height. In 16 cases the R-wave became markedly higher on inspiration; in 1 case inspiration resulted in notching of the R-wave. In 5 cases the R-wave was notched; in 5 cases the height of the R-wave changed with change in position.

The S-wave was present and distinct in 29 cases, in 14 of these it was somewhat slurred. In 15 cases it changed with change in position; in 12, it was greater in Position 1 than in Position 2, and in 3 it was greater in Position 2 than in Position 1. In addition to the 4 cases of transverse

heart as evidenced by inverted Q-waves there were 7 cases of transverse heart in which the inverted wave was clearly an S-wave. In 7 cases the inversion was deep enough to be called left axis deviation. Deep inspiration affected the wave in 14 cases, in 11 cases it became shallower, in 3 cases it became deeper. In 1 case it apparently changed from a negative to a positive wave on deep inspiration. S-waves were absent from Lead III in 21 cases.

*T-Waves.*—In Leads I and II no T-waves were inverted. In 2 cases the T-waves were iso-electric in Lead I, Position 1; in both of these they were upright in Position 2. In 1 case they were diphasic in Lead II, Position 1, but became entirely upright in Position 2 (in this case the T-wave was inverted in Lead III, more in Position 1 than in Position 2).

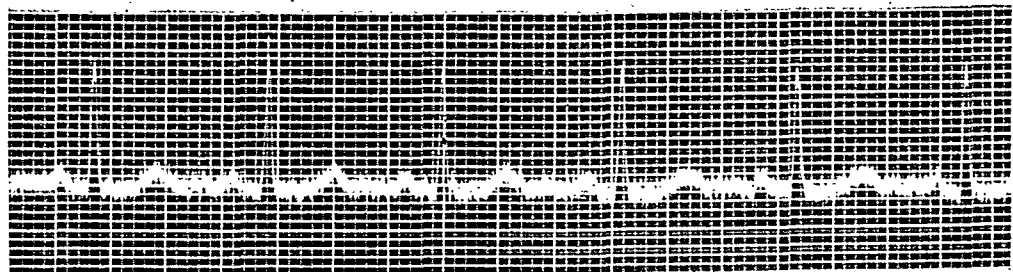
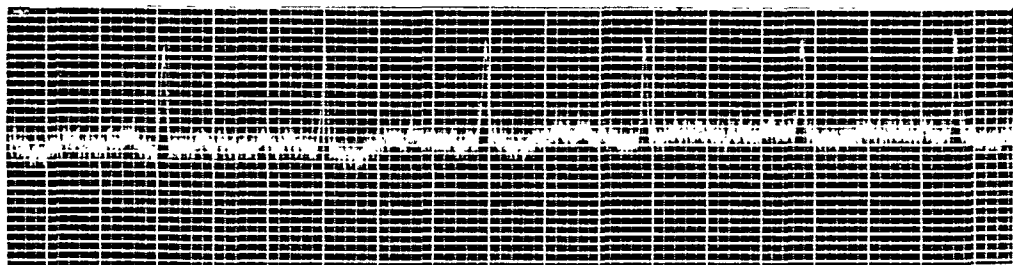


Fig. 5.—Case 6, Lead II, Positions 1 and 2, showing change of T-waves with change of position.

In 15 cases the T-waves were upright in all leads. In 2 of these the T-waves in Leads II and III were greater in Position 2 than in Position 1. In 25 cases the T-waves were upright in Leads I and II; in 14 of these they were iso-electric in Lead III, in 5 they were diphasic in Lead III, and in 6, inverted in Lead III; of these 6, 3 were more inverted in Position 1 than in Position 2.

Change in position affected the T-waves: in Lead II they were in 3 cases higher in Position 2 than in Position 1; in 1 of these the T-wave in Lead III was indeterminate in Position 1 while it became upright in Position 2, in another case the T-wave in Lead III was diphasic in Position 1 and became upright in Position 2.

In general, it was concluded that the T-waves showed very few changes in Leads I and II, but that in about half the cases the T-waves showed in Lead III changes from the simple upright shape.

*Measurements.*—Three time intervals were measured; the P-R interval, the duration of the QRS complex, and the S-T interval. All measurements fell within normal limits.

Of the P-R intervals 43 were between 0.15 and 0.19 seconds; 3 were 0.20, and 4 were 0.12 to 0.14.

Of the QRS complexes 43 were between 0.06 and 0.08 seconds, 3 were 0.09, and four were 0.04 to 0.05 seconds.

Of the S-T intervals, 47 were between 0.26 and 0.32 seconds, the other 3 readings were 0.24, 0.34, and 0.36 seconds.

There was thus no tendency to prolongation of any intervals, especially not to spreading of the QRS complex.

#### DISCUSSION

The question may be raised whether all of the patients in this series really had undamaged hearts. If it is true, as Fahr<sup>3</sup> states, that 23 per cent of deaths among persons past fifty years of age are caused by heart disease it is not unlikely that some persons in this series had myocardial disease which had not yet caused symptoms or physical findings. Then among, say, any 60 persons past fifty years of age, 14 may statistically be expected to die from heart disease. But if we exclude from the 60 those among the 14 who have manifest symptoms of heart disease or abnormal findings, such as increased blood pressure, cardiac enlargement, murmurs or cardiac irregularities, and those who have not yet developed any pathological process, and who, therefore, must be considered healthy, the chances are, that after such analysis we shall be left with a series of about 50 persons among whom very few have "hidden" heart disease. We believe that the electrocardiograms just described are from such a series. Therefore, in the absence of any changes which we know by experience are associated with grave cardiac disorders, the findings of this series may probably be considered such as occur in normal persons. On the other hand, the absence of certain findings from the series should cause these to be looked upon with suspicion as possibly indicating cardiac pathology.

#### SUMMARY

Within the limits of our experience we may state:

The following findings, some of which we have previously considered of doubtful significance, are not pathological.

Diphasic or iso-electric P-waves in Lead I or inverted P-waves in Lead III, if they become upright on deep inspiration; slurring of QRS complexes, especially in Lead III and slight to moderate notching of R with the QRS interval below 0.10 seconds, "transverse heart," isolated left axis deviation, moderate inversion of T-III (this last finding is very common).

On the other hand, the following findings were not present in this series and must therefore be looked upon with suspicion.

Indeterminate or inverted P-waves in Leads I or II, inverted P-waves in Lead III, if they do not become upright on deep inspiration. Inversion of T-waves in Leads I or I and II, or iso-electric T-waves in Leads I or II if they do not become upright on deep inspiration. A P-R interval exceeding 0.20 seconds, a QRS interval exceeding 0.10 seconds, or an S-T interval exceeding 0.34 or 0.36 seconds (the upper limit seems slightly uncertain).

It is seen that for the proper evaluation of a doubtful finding deep inspiration and sometimes change in position may be necessary in any lead. Such thorough investigation should always be done when the electrocardiographic findings may be the determining factor in the diagnosis.

This material does not indicate whether an isolated right axis deviation is definitely a pathological sign or whether the inverted wave in a transverse heart is always an S-wave.

There do not seem to be any characteristic "age-changes" in the electrocardiogram.

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# VENTRICULAR TACHYCARDIA: AN INTERPRETATION OF THE NATURE OF ITS MECHANISM\*

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THE stroke volume output of the mammalian ventricle is largely dependent upon a uniform and nearly simultaneous contraction of all parts of its musculature. This is brought about by the highly specialized His-Tawara-Purkinje system with its specific anatomical arrangement and conduction capacities. From the A-V node the excitation proceeds by the bundle branches to both chambers and spreads through the rapidly conducting network of Purkinje to all parts of the ventricles. This plan of transmission is in contrast to that in the auricles where the excitation is distributed by direct propagation through the more primitive arrangement of the muscle bands.

Tachycardia, flutter, and fibrillation of auricular origin are considerably more common than are the similar phenomena in the ventricles. In a previous study of ventricular fibrillation<sup>1</sup> it was suggested that the probable explanation of this discrepancy lies in the normal preventive and regulatory action effected through the His-Tawara-Purkinje system; that its capacity to distribute supraventricular impulses very quickly to all regions of the musculature not only insures harmony of contraction but further creates a uniform state of refractoriness which in itself tends to resist the setting up of circus movements in these chambers. An ectopic impulse tending to perpetuate itself through a process of reexcitation would theoretically be frustrated by a supraventricular impulse which at the opportune moment spreads through the normal path to all parts of the ventricle and induces a state of refractoriness sufficient to block the path of the re-entrant excitation. This would account for the rarity of continuous runs of ectopic beats in healthy individuals, for isolated premature beats are common, and in psychoneurotic individuals, a bigeminal rhythm is not infrequent. If the presence of frequent premature beats may be taken as an expression of hyperirritability of the ventricles, an explanation of the occurrence of ventricular tachycardia based on this factor alone would appear inadequate.

In bundle-branch block the ventricle corresponding to the side of disease receives its excitation from the adjacent ventricle by direct propagation through the septum. The spread is similar to that present in the ventricular premature beat. So long as conduction is still satisfactory through one bundle branch, the rhythm may continue to be governed through the A-V node. When conduction, however, is seriously impaired in both bundle branches, conditions are opportune for the development of circus movements, or tachycardias. The coordinating and regulatory function of the His-Tawara-Purkinje system is lost;

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the path through which impulses normally interrupt a sequence of ectopic beats is impaired; and the ventricles are exposed to any aberrant excitation. In the event of complete failure of nodal activity, and in the absence of a spontaneous excitation in the musculature, ventricular standstill ensues.

Explanations for the development of ventricular tachycardia have generally failed to give full consideration to the state of the conducting tissues and have invariably emphasized the condition of the myocardium, a hyperirritability induced by underlying disease, digitalis, or a combination of both. In the present communication attention is called to the fact that disorders of the ventricular rhythm such as tachycardia or flutter fibrillation are in many instances intimately related to direct interference with the His-Tawara-Purkinje system of conduction, and that disease of the bundle tissues, or depression of these tissues by drugs is an important precursory state in their development. The same interpretation as related to ventricular fibrillation or flutter fibrillation was emphasized in 1926 by DeBoer<sup>2</sup> and in 1929 by Davis and Sprague.<sup>1</sup> Six cases of a total of 14 with ventricular fibrillation reported up to 1929 were associated with heart-block. In two cases the abnormal rhythm was probably induced by digitalis, in one of these digitalis in combination with quinidin.

An examination of the reported cases of ventricular tachycardia also reveals evidence of bundle tissue disease, or the action of drugs that depress these tissues in a large number. Most of the reported cases were associated with the following conditions: (1) digitalis poisoning, (2) bundle tissue or bundle-branch disease, (3) coronary thrombosis. Rare cases are reported to have occurred in young adults with little or no demonstrable organic heart disease,<sup>3, 4, 5, 6</sup> in patients with rheumatic and syphilitic heart disease, and possibly as a result of excessive tobacco smoking.<sup>7</sup>

#### THE RELATION OF DIGITALIS TO VENTRICULAR TACHYCARDIA

In studying the progressive action of increasing doses of digitalis on the cat's heart, Robinson and Wilson<sup>8</sup> found the following sequence of events: inversion of the T-wave of the electrocardiogram; depression of the atrio-ventricular conduction with some slowing of the heart rate; increased rhythm of both auricles and ventricles with complete A-V dissociation, the ventricular rate soon exceeding the auricular. After complete A-V dissociation idioventricular complexes made their appearance, and independent ventricular rhythms with abnormal ventricular complexes occurred. This was followed by ventricular fibrillation and death. Luten<sup>9</sup> and others have shown that digitalis poisoning in man produces the same sequence of changes observed by Robinson and Wilson in cats. Commenting on an analysis of four cases in which ventricular tachycardia developed in the course of digitalis poisoning, he states, "It would appear, therefore, from a consideration of these four cases,

that toxic doses of digitalis produce on the human heart, when administered in increasing amounts, the following sequence of abnormal mechanism: auricular tachycardia; increase in the ventricular rate until it exceeds the auricular rate; and independent ventricular tachycardia with abnormal complexes." In his cases prolongation of the A-V conduction time was an early effect, and the increased ventricular rate always followed complete A-V dissociation. This association and sequence is significant, for it points to the importance of the state of bundle tissue in the course of development of the abnormal ventricular rhythm.

Vaughn<sup>10</sup> reported two cases of ventricular tachycardia associated with the administration of full doses of digitalis and considered it the probable factor responsible. He noted that although ventricular premature beats were frequent and the use of digitalis was common, runs of premature beats or tachycardia was rare. In 189 cases at the Peter Bent Brigham Hospital with the diagnosis of premature beats, he found but seven or 4 per cent with successive extrasystoles. Sixty-three per cent of the cases in this series had received digitalis, but in a large proportion digitalis administration was begun after the tracings were taken. In subsequent tracings no increase in the number of extrasystoles occurred. Vaughn concluded from this analysis that digitalis in therapeutic doses does not increase the tendency to successive ventricular extrasystoles. A similar conclusion was reached by Otto and Gold<sup>11, 12</sup> who felt that digitalis in full doses sometimes abolishes ventricle premature beats, and that premature beats coming spontaneously or induced by digitalis do not indicate susceptibility to digitalis bigeminy. Vaughn suggested that digitalis may be an exciting cause in the production of ventricular tachycardia but that some other factor such as hyperirritability resulting from impaired blood supply must be present. In one of the two cases reported by him bundle-branch block (P-R 0.20; QRS 0.12) was present before the administration of digitalis, and in this case it is probable that two factors were operative: (1) the underlying disease of the bundle tissue; (2) the depression of these tissues by digitalis. The conclusions by Vaughn, and Otto and Gold regarding the relation of normal doses of digitalis to premature beats lends further weight to this interpretation.

Tachycardia of ventricular origin associated with full or toxic doses of digitalis has been reported by many observers including Gilchrist<sup>7</sup> (two cases), Schwensen<sup>13</sup> (two cases), Felberbaum<sup>14</sup> (one case), Reid<sup>15</sup> (five cases), Levine and Curtiss<sup>16</sup> (one case), Gallavardin<sup>17</sup> (one case), Howard<sup>18</sup> (one case), Palmer and White<sup>19</sup> (two cases), Marvin<sup>20</sup> (five cases), and Strauss<sup>21</sup> (two cases). In one of Gilchrist's cases there was evidence of pre-existing disease of the bundle tissue with a P-R interval of 0.31 before the administration of digitalis. Smith, Schwensen and Gilchrist stressed the action of digitalis on the ventricular muscle as the precipitating factor. Smith thought that the action of digitalis

was variable and that the state of the heart muscle must be the deciding factor; Schwensen, that digitalis probably induces irritability in the ventricles; and Gilchrist, that the action of digitalis on a malnourished ventricular muscle might be the combination of factors responsible. In most of the reported cases in which there are tracings of the normal rhythm before and after the onset of the tachycardia, a marked prolongation of the P-R and often of the QRS interval is to be observed. Smith noted that of 60 reported cases, digitalis had been administered and was probably the responsible factor in 25. Strauss recorded digitalis therapy in 50 per cent of 65 cases reported up to 1930. Three out of a group of six cases with this arrhythmia among electrocardiographic records of the Beth Israel Hospital during the years 1928-1932 were definitely associated with excessive doses of digitalis. In one of these there was evidence of underlying bundle tissue disease.

#### THE RELATION OF BUNDLE TISSUE DISEASE TO VENTRICULAR TACHYCARDIA

As records of the normal electrocardiogram, either before or sufficiently after the administration of digitalis were not reported in all cases, it is impossible to obtain an exact idea as to the frequency of pre-existing bundle tissue disease in the digitalis cases. If conduction disease of the main bundle (P-R interval) had been present, this would be obscured in many, as the P-R interval was seen to be greatly increased in the postparoxysmal records. However, evidence of pre-existing bundle-branch disease was noted in 5 instances in the group receiving digitalis. The cases of Vaughn and of Gilchrist were mentioned above. In one of Marvin's cases there was pre-existing bundle-branch block with a P-R interval of 0.20 and a QRS interval of 0.12 seconds. Necropsy examination of the bundle branches in serial section showed definite disease in one bundle, thus confirming the electrocardiographic findings. Bundle-branch disease may also have been present in one of Palmer and White's cases, the QRS interval measuring 0.12 seconds.

One case reported by Butterfield and Hunt<sup>22</sup> occurred in a man aged forty-five years with rheumatic heart disease. The electrocardiogram showed a P-R interval of 0.18 and a QRS interval of 0.13 seconds. Postmortem examination revealed thickening of both mitral cusps, lymphatic infiltration, and an increased amount of connective tissue in the region of the bundle. The chief changes were found in the region of an antemortem clot adhering to the left side of the septum, and here an active pathological process was in progress at the time of death. The most important changes involved two-thirds of the thickness of the interventricular septum and consisted of a progressive fibrosis involving the muscle to such an extent that very few cardiac fibers could be recognized as such throughout a considerable amount of tissue. The increase in the QRS interval in this case was due either to involvement of the bundle branches or conceivably to block in the spread of excitation shortly after leaving the bundle branches in the

septum. Hart<sup>23</sup> reported one case in 1912 with unquestionable ventricular tachycardia. The interparoxysmal records show a P-R interval of 0.25, a QRS interval of 0.15 seconds. At the time of the paroxysm, the patient was on a small amount of digitalis, but when digitalis was out of the system the evidence of bundle-branch block was present. One case reported by Willius showed a P-R interval of 0.25, and a QRS of 0.10 seconds. In another case, in the same author's series, evidence of so-called "arborization block" is present. In Porter's<sup>24</sup> case associated with an attack of coronary thrombosis, the P-R interval was 0.22, the QRS interval 0.12 to 0.13 seconds. There was no indication of the use of digitalis. In one of Levine's cases<sup>6</sup> of ventricular tachycardia complicating coronary thrombosis definite bundle-branch block was present.

Two cases taken from the records of the Beth Israel Hospital showed ventricular tachycardia associated with bundle disease in the absence of digitalization. One case presented partial A-V block with P-R intervals as long as 0.42 seconds. In this case the paroxysmal ventricular complexes differed but slightly from the normal, suggesting the origin to be in the main bundle tissue. The second case occurring in a patient with coronary thrombosis in the past showed a P-R interval of 0.21, a QRS interval of 0.12 seconds.

#### THE RELATION OF VENTRICULAR TACHYCARDIA TO CORONARY THROMBOSIS

A number of cases of ventricular tachycardia are now on record as complicating an attack of acute coronary thrombosis. In most of these cases the conduction time in the tracings preceding and following the paroxysm is normal. It is known that the septal muscle receives its excitation slightly in advance of that of the outer walls of the ventricles and less than one-tenth of a second is required before all parts of the muscle are in a state of activity. For practical purposes this distribution is nearly simultaneous. The slight difference, however, in the time from the moment the excitation arrives at one place and is finally distributed at all points is probably represented by the QRS interval and when this is normal it is probable that there is little gross interference with the His-Tawara-Purkinje distribution. Yet for the occurrence of ventricular tachycardia in a condition in which the function of varying areas of heart muscle is disturbed, and in a condition in which the septum is often the site of involvement (the anterior descending branch of the left coronary being frequently involved), an explanation must consider the possibility of temporary disturbances in the conduction tissues. Although an infarct may not interfere with the endothelial transmission of impulses in the Purkinje network, there may be moments when the development of local edema or mural thrombosis causes such interference. The presence of large infarcts or mural thrombi in many of the cases developing ventricular tachycardia following coronary thrombosis is suggested by the outcome in Levine's series of 8 cases. Six died, in spite of the fact that the tachycardia was

regularly controlled by quinidine. It therefore seems reasonable to consider a factor of this kind in addition to the factor of local hyper-irritability in the muscle.

#### THERAPEUTIC CONSIDERATION

The action of quinidine in the abolition of attacks of ventricular tachycardia has been recorded in many cases. Lewis and his coworkers<sup>25</sup> studied in the action of quinidine in dogs. An early and marked effect was produced in the heart muscle, and this consisted in a slowing of the rate of conduction and an increase in the refractory period. The action on the conduction tissues was also striking, a lengthening of the P-R and QRS intervals being regularly noted with sufficient dosage. There is evidence that in man a powerful action may be exerted on the muscle before an appreciable effect on the conducting tissue is noted. Thus, after the abolition of auricular fibrillation in clinical cases, the electrocardiogram often shows no appreciable increase in the P-R and QRS intervals. It is therefore probable that quinidine exerts its action on the ventricular muscle to the extent of interrupting a tachycardia without causing significant depression of the bundle tissues in most cases. In rare instances and when bundle tissue disease is present, quinidine may precipitate fibrillation of the ventricles by exerting a predominant action on the conducting tissue. This probably occurred in the case of Kerr and Bender.<sup>26</sup>

On the basis of the above, it would seem that digitalis therapy should be undertaken with caution in the presence of bundle tissue disease. Drugs which tend to increase conduction might be considered in the attempt to stop a paroxysm of ventricular tachycardia. Atropine, by diminishing vagal action may be of value. Levine<sup>27</sup> has had one success with this drug. On theoretical grounds, adrenalin, ephedrin, barium chloride and thyroid extract might be of value, in sufficient dosage. When combined with quinidine the untoward effect of these drugs on the ventricular muscle might be controlled.

#### SUMMARY AND CONCLUSIONS

1. An interpretation of the mechanism of ventricular tachycardia is presented: Its occurrence in healthy individuals is normally prevented by the control effected through the His-Tawara-Purkinje system of conduction, which distributes supraventricular impulses very rapidly to all parts of both ventricles and induces a uniform state of refractoriness sufficient to prevent the setting up of continuous runs of ectopic beats. Disease or drugs that depress the conducting tissues tend to interfere with this normal control and permit the development of circus movements in the ventricles.

2. An analysis of the literature reveals the presence of disease or the use of drugs which depress the conducting tissues in a majority of the reported cases.

3. Ventricular tachycardia resulting from digitalis is probably induced by its depressing action on the conducting tissues, and this factor must be considered together with hyperirritability of the muscle.

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## CARDIAC RUPTURE WITH PERFORATION OF INTERVENTRICULAR SEPTUM. REPORT OF TWO CASES\*

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**R**UPTURE of the heart is moderately frequent following thrombosis, but perforation is usually through the wall into the pericardium, rupture of the septum being exceedingly rare. The event of interventricular rupture is accompanied by sufficiently characteristic symptoms and signs to make the condition recognizable ante mortem. There are, however, certain similar conditions that have to be differentiated, namely, external rupture of the heart allowing blood to pass through into the pericardium, and ruptured aneurysm of the right anterior aortic sinus causing a communication between the aorta and the base of the right ventricle. The latter condition may be of congenital origin, the clinical evidences of its presence existing throughout life, but in far the greater number of cases (Abbott) it results from rupture of an aneurysm of the aorta into the pulmonic circulation.

The cases of spontaneous cardiac rupture collected by Krumbhaar and Crowell showed the following distribution, the great majority being through the wall of one of the cardiac chambers into the pericardial cavity.

TABLE I  
SITE OF SPONTANEOUS RUPTURE (KRUMBHAAR AND CROWELL)

|                 | TOTAL | PER CENT |
|-----------------|-------|----------|
| Right auricle   | 35    | 5.7      |
| Left auricle    | 12    | 2.0      |
| Right ventricle | 63    | 10.2     |
| Left ventricle  | 493   | 79.7     |
| Miscellaneous*  | 15    | 2.4      |

\*The miscellaneous group consists mostly of ruptured papillary muscles but includes the two cases of rupture reported by Latham.

Three typical cases of interventricular rupture have previously been reported. Abstracts of these cases are given.

CASE 1. (Latham.) White male, aged sixty-one years, of gouty diathesis and sedentary habits, complained of unusual pain occupying entire front of chest and passing along both clavicles to the top of the shoulders, stopping there without descending the arms. Pain remained constant for two days but became more severe during the last night. The pulse was normal in rate but hard and incompressible as it had been for a long time. A mustard plaster was applied and some cordial aperient given. No relief was obtained next day, the patient having been sleepless and unable to lie down. The heart beat over a larger space with more force than natural but with no unnatural sounds. The pain was like that of angina pectoris but continuous. One-half dram of vinum colchici and one dram of paregoric were

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duodenal ulcer was made and operation advised. Relatives objected and two hours later another physician noted the patient's desperate condition and very feeble heart action. Four hours after the onset the patient was seen by Hyman. The patient was now in extreme shock with cold, clammy perspiration, deeply cyanosed and breathing with noisy respirations. There was no palpable pulse at wrist, and the superficial area of cardiac dullness appeared widened to percussion. No heart sounds could be heard at the apex but the basal sounds were rapid (130 per minute) and of very poor quality. There was a very shrill systolic murmur heard equally well over the entire precordia. A diagnosis of spontaneous rupture of the heart was made and hospitalization advised. The patient was admitted to the hospital at 11:30 A.M., electrocardiographic studies were made and intravenous glucose and metaphyllin administered. The heart sounds now became more audible at the apex as well as at the base, but the superficial character of the murmur remained unchanged. The patient died half an hour later, death occurring five and one-half hours after the initial attack of pain.

Electrocardiographic studies showed characteristic T-wave alterations in Leads I and II. There was no axial deviation of heart and no delay in the QRS complex. The rate was 100 beats per minute. Sino-auricular rhythm was normal.

At postmortem examination the pericardium was found free from blood. The heart was slightly enlarged (310 grams), and there was a recent perforation large enough to admit one finger in the interventricular septum near the apex. The coronary arteries contained irregular patches of sclerosis; the right was more involved than the left. A rather large thrombus which had apparently broken off from an adjacent area was found in the terminal subdivision of the anterior descending branch of the right coronary artery. The portion of the heart supplied by this vessel was pale, thinned out, and the change appeared to be not very recent. The apical part of the heart, especially in the right ventricle, contained a large hemorrhagic area which was torn through as it approached the septum. Several mural thrombi were found in the left ventricle. The valve mechanism presented nothing of note, and the aorta was not enlarged but showed many atheromatous plaques.

In addition to the cases of septal perforation following myocardial infarction, communication between the two ventricular cavities or between the aorta and the base of the right ventricle may develop in a somewhat different manner.

Abbott's study of abnormal communications between the aorta and the base of the right ventricle or between the aorta and the pulmonary artery is interesting because of the similarity of the symptomatology to that of our cases and the difference in pathology. She points out that a communication may arise in two ways: (1) as the result of a ruptured aneurysm where the wall of the ascending aorta is extensively diseased from luetic or other causes; (2) when the right anterior aortic sinus is the seat of a finger or thimblelike process which projects into the conus of the right ventricle. This constitutes an aneurysm of its wall and that of the aortic sinus due not to disease but apparently to congenital thinning of the septum between the two great trunks. This latter explanation may be applied to the cases of Beck, Hale-White, Krzywicki and Kraus in which the walls of the aneurysm were thin and membranous without sign of inflammatory process of any kind and rupture had taken place at the apex of the sac, evidently as a result

acute aortic stenosis was considered, such as the formation of a mural thrombus in the left ventricle obstructing the aortic outlets of that chamber. Other diagnoses considered included ruptured aortic leaflet and also the formation of a dissecting aneurysm. Ruptured aortic leaflet was not considered seriously on account of the fact that this would not obstruct the forward propulsion of blood. The next day the patient developed evidence of a mild hypostatic pneumonia, grew gradually weaker, and died that night, April 17, at 8:30 P.M. A final diagnosis of coronary thrombosis and hypostatic pneumonia was given.

Electrocardiographic studies showed tachycardia, left ventricular preponderance and a convex inverted T-1. The manner in which the T-wave took off below the base line in Leads II and III suggested coronary occlusion (Fig. 1).

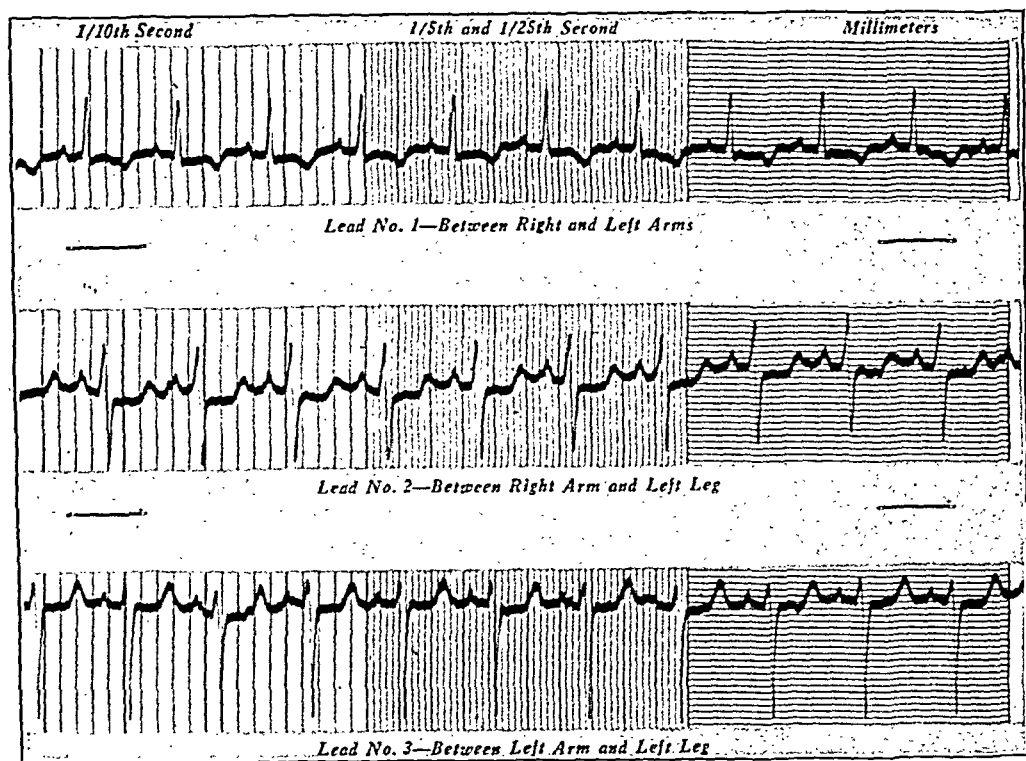


Fig. 1.—(Case 1.) Electrocardiogram taken April 16, showing left ventricular preponderance and a partial "coronary T-wave."

Necropsy disclosed generalized arteriosclerosis with nephrosclerosis and multiple infarcts of the brain; passive congestion of all the organs and intense congestion and edema of the lungs without pneumonic consolidation or pleural effusion. The heart weighed 545 grams. The pericardial cavity contained very little fluid. The right ventricle appeared particularly dilated and was filled with partially decolorized clots. The wall was rather pale but normal in consistency and texture. The right atrium was distended with partly decolorized clots and the auricle contained an adherent thrombus. Dark, soft, currant-jelly clots were found in the veins leading into the right atrium. The left ventricle was thickened posteriorly but was thin and rather fibrosed anteriorly. The myocardium had a rather dull red beefy color, was quite fine in texture and showed little or no fibrosis externally. The left atrium was not particularly dilated and its appendage was collapsed. There were mixed clots in both atrium and ventricle, and soft red clots in the pulmonary veins. The wall of the left ventricle measured 25 mm. in thickness, the right 5 mm., the circumferences of the valvular orifices were as follows: aortic 8.5 mm., mitral

10.5 mm., pulmonic 9 mm., tricuspid 14 mm. The valves on the right side of the heart were quite normal in character, although the tricuspid orifice seemed dilated; the mitral valve was slightly thickened and sclerotic but fairly flexible. The leaflets of the aortic valve were definitely thickened, showed bits of calcareous material at their bases and projected rather rigidly into the lumen, but not sufficiently to cause obstruction to the forward flow of blood. They were competent to the water test. The coronary arteries showed marked atheromatous degeneration with calcification. Wherever one of these was cut through with the scissors or knife, there was a crunching or grating sound. The changes were most marked in the anterior descending branch of the left coronary artery which was thicker in parts than a lead pencil and which showed almost complete obliteration of the lumen. On account of

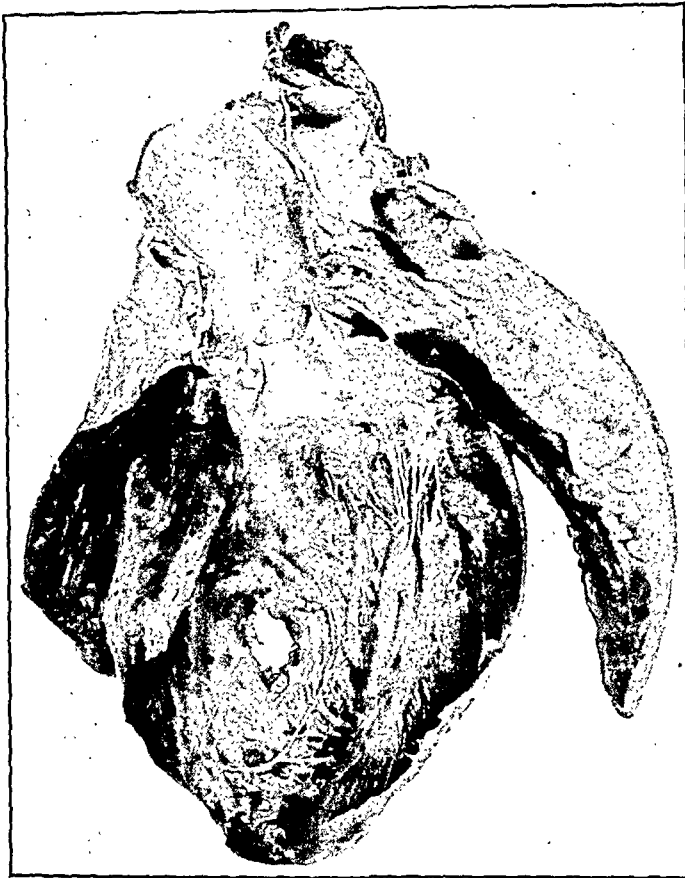


Fig. 2.—(Case 1.)—Photograph of the heart showing septal perforation in the middle of an aneurysmal bulging.

a desire to preserve the specimen it was not dissected free. The other coronary branches were sclerotic to a lesser degree.

Upon opening the left ventricle there was found an area of dilatation in the lower part near the septum, with separation of the pectinate muscles and columnae, forming an aneurysm 7 to 8 cm. in diameter, the walls of which were smooth, flat and covered by thick whitish endocardium. In the center of this was a much deeper depression, dark in color, with somewhat ragged torn edges and a little reaction surrounding it. The tip of the index finger passed easily through this perforation into the cavity of the right ventricle within 2 cm. of the tip of the latter. Rather intimately applied to this, on the right side there was a thick membrane made up of fibrin and fresh thrombus, attached to the lateral wall of the right ventricle and partially covering the opening. Some of the columnae carneae were not yet broken down in this vicinity and gave added foundation for the thrombus. When the heart

was held up to the light and the columnae carnae retracted, it was easy to see from one ventricle into the other. There was a moderate bulge of the septal wall into the right ventricle, most marked in the region of the perforation (Fig. 2).

CASE 2. White female, aged seventy years, a resident of various mental institutions since 1904, had good physical health until 1914 when she was operated on for hernia. In 1915 she fractured her right hip and was very lame for the rest of her life. During 1926 she suffered somewhat with bronchitis and laryngitis and in 1929 was hospitalized for a time because of dysuria and hematuria and again in 1930 for herpes zoster which was followed by severe anemia. Suddenly during the night of June 1, 1931, the patient developed acute abdominal pain necessitating the use of morphine. On examination the following morning the patient was fully conscious

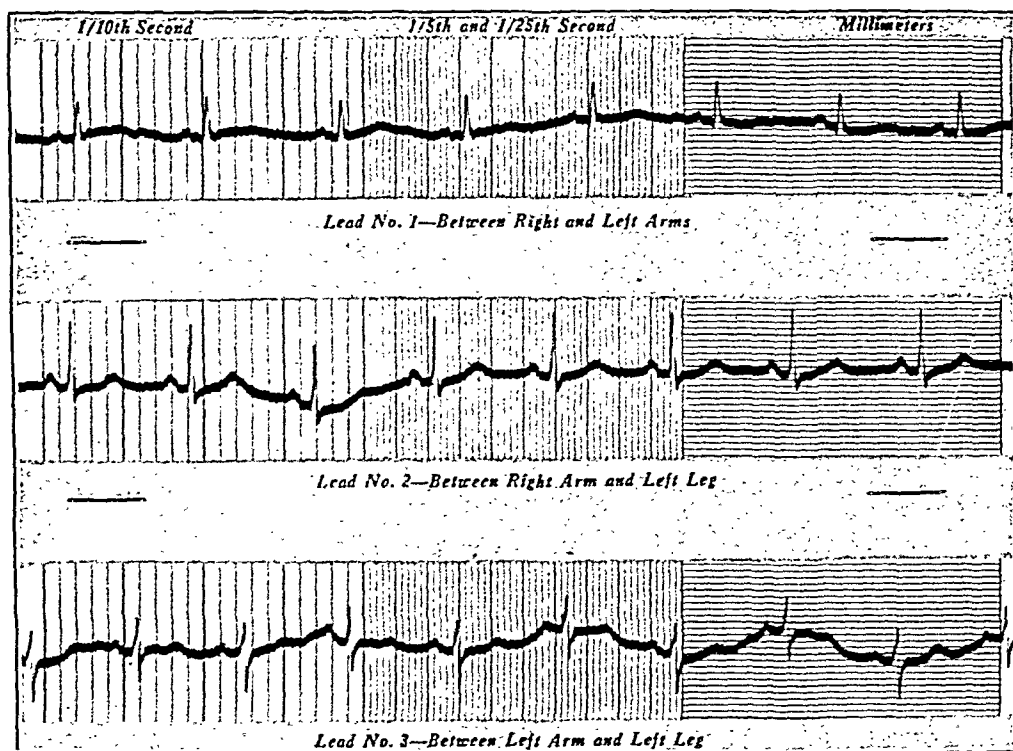


Fig. 3.—(Case 2.) Electrocardiogram taken June 2 showing partial "coronary T-wave" in Leads II and III.

and complained of severe intermittent pain of a stabbing character which seemed to be localized across the upper abdomen and under the left costal margin. She also complained of pain in the left arm and upper interseapular area. The patient yawned occasionally. Her skin was pale and she appeared to be in shock. Morphine was administered but the discomfort and pain were not entirely relieved. There was no cyanosis of any part of the body, but slight edema of the ankles was present. Examination of the chest revealed no impairment of percussion note over the lungs. There were numerous coarse râles over both bases posteriorly, more marked on the left side. The area of cardiac dullness was not appreciably enlarged and auscultation revealed regular cardiac rhythm and no murmurs. The peripheral arteries were slightly tortuous. Blood pressure was systolic 150 mm., diastolic 60 mm. The liver was not palpable. Diagnosis of an acute coronary occlusion was made. Electrocardiogram substantiated this by the low take off of T-2 and T-3 (Fig. 3).

The patient continued to suffer the above described pain for two days and vomited occasionally. On the third day her temperature became elevated and continued so

until her death. On the fourth day of her illness examination revealed a well-marked systolic thrill, and a loud systolic murmur over the entire chest and a systolic blood pressure of 80 mm. The thrill and murmur became more pronounced on the following day. The patient grew gradually weaker and died June 7, 1931, at 2:12 P.M.

A final clinical diagnosis of coronary thrombosis and generalized arteriosclerosis was made.

Necropsy disclosed generalized arteriosclerosis with passive congestion particularly marked in the lungs and associated here with thrombosis and multiple hemorrhagic infarcts. The kidneys showed arteriosclerosis with multiple infarcts and a hypernephroma invading the pelvis on the left side. The gall bladder was contracted



Fig. 4.—(Case 2.) Photograph of the heart showing a match inserted into the interventricular perforation.

around two stones; there was a colloid cyst of the thyroid; the brain was atrophic but not particularly arteriosclerotic.

The pericardial cavity contained a small amount of dark amber fluid. The heart weighed 435 grams, but appeared much larger owing to marked dilatation. The epicardium was smooth and thin, rather liberally supplied with fat. The right atrium was markedly distended with mixed clots, but no thrombi were found in the appendage; the tricuspid orifice appeared normal and the leaflets were thin and flexible. The right ventricle contained fairly firm, partially decolorized clots that became more adherent in the lower portion, especially to the septum. The lateral wall of the right ventricle was of good color and consistency, but the septum appeared pale and soft, with hemorrhagic areas here and there. A small perforation was found within about 2 cm. of the apex. This admitted a match (Fig. 4), although

the area of ragged laceration was somewhat larger and definitely greater on the side of the left ventricle. The area of anemic and hemorrhagic necrosis measured about 4 cm. in diameter, and there was a thinning of the septum around the point of perforation, but very little aneurysmal bulging was observed. The apex of the left ventricle was dilated in aneurysmal fashion, with a thin, somewhat fibrous wall, and thickened endocardium, but organized thrombi were not found on this side of the heart. The perforation was partly sealed off by the adherent thrombi and clots on the right side of the heart. The valves showed no abnormalities. The coronary arteries were rather tortuous and showed atheromatous patches, especially marked in the anterior descending branch, but the location of the thrombus was not further investigated (Fig. 4).

#### DISCUSSION

Interventricular rupture like other ruptures of the heart occurs in middle or old age and is preceded by coronary disease with occlusion of a branch supplying the interventricular septum. Clinically the rupture is usually preceded by an acute illness in which all the symptoms may point toward some grave abdominal condition, as in Hyman's case where a diagnosis of ruptured gastric or duodenal ulcer was suggested and in our second case where the first complaint was of severe abdominal pain. Or the symptoms may at first simulate a respiratory disorder with dyspnea, cyanosis, fever and leucocytosis, as in our first case. Finally, the symptoms may attract attention to the heart from the beginning by severe pain in this region which may or may not radiate down the arms, as in Latham's two cases. In this initial period no diagnosis of septal perforation can be made whether or not the attention is attracted to the cardiac mechanism. Examination of the heart at this time may be entirely negative or may indicate anginal failure. Electrocardiographic tracings may indicate coronary occlusion or myocardial fibrosis. Murmurs are usually absent, and the history usually shows fair health prior to the acute onset. The persistence of the symptoms, however, especially the pain, reveals the seriousness of the patient's condition, and the striking change in the patient and clinical findings following the rupture should make this condition distinguishable from other complications.

Perforation of the interventricular septum is ushered in by renewed syncope, by an increasingly harsh systolic murmur and thrill with gradual extinction of the aortic second sound, progressive fall in blood pressure with obliteration of the pulse, ashen pallor rather than cyanosis, and pulmonary inundation. The disproportion between the force of the cardiac impulse and the quality of the pulse, together with the increasing thrill and murmur and the absent second sound would appear to be particularly suggestive of septal perforation.

The elapsed time from the onset of symptoms until rupture of the septum, according to a survey of the five cases at hand, varies from two days to six weeks.

Rupture of the heart into the pericardium usually causes instantaneous death, or the patient may go into profound shock and die in a few hours.

The length of life is somewhat longer, however, following interventricular rupture as shown in Table II.

TABLE II  
LENGTH OF LIFE AFTER INTERVENTRICULAR RUPTURE

|                     |           |
|---------------------|-----------|
| Latham's case No. 1 | 17 hours  |
| Latham's case No. 2 | 3 days    |
| Hyman's case        | 5½ hours  |
| Our case No. 1      | 38½ hours |
| Our case No. 2      | 1½ days   |

Rupture of an aneurysm of the right anterior aortic sinus of Valsalva occurs suddenly in a person in apparently perfect health, and the patient may survive the rupture for years, the accompanying precordial thrill and murmur persisting unchanged. Furthermore, the rupture of such aneurysms occurs in relatively young individuals. The symptoms in such individuals are usually less serious because of the better condition of the musculature of the heart. The sudden diverting of part of the blood stream from the systemic circulation through the septum into the lesser circulation is followed by considerable strain upon the musculature of the right ventricle. A healthy musculature will be able to compensate for this added load, and the heart will continue to function in a satisfactory manner; but if the muscle is already diseased, congestive failure develops in the lesser circulation.

The location of the perforation itself probably has little effect upon the electrocardiographic tracing, but it is interesting that no more serious or specific changes are present. The location of the septal infarction would appear to be sufficiently distal to permit the main conduction bundles to escape. The higher in the septum the infarct extends, the more profound are the observed electrocardiographic alterations.

The rarity of septal perforation in comparison with external perforation would seem to be due to the relative freedom of the septum from marked changes in the pressure applied to the two sides. While the pressure within the left ventricle probably rises to some 200 mm. Hg in the normal heart, this is compensated on the other side of the ventricle by a pressure probably half as great. In cases of coronary occlusion there is undoubtedly a distinct fall in the intracardiac pressure in both chambers, but the ratio of left to right would probably show less pronounced alterations. Thus the integrity of the septum would tend to be preserved. Indeed, infarction of the septum is by no means rare, but its perforation would appear to be almost a curiosity.

The clinical picture of pallor, pulselessness, Cheyne-Stokes respiration, absence of the aortic second tone, in conjunction with a loud systolic murmur which is out of all proportion to the character and intensity of the other heart sounds and a forceful action of the heart indicates that there is something preventing the forward propulsion of the blood. In

view of the pathologic condition it is easy to see that the development of shock with deficient circulation, a loud systolic murmur and thrill, and no pulse, would result from blood in the left ventricle being forced through the septum into the right ventricle through a roughened orifice. This is brought about by the fact that the pressure is physiologically highest in the left ventricle. Pallor and shock rather than cyanosis result because the blood is propelled into the lungs from both chambers of the heart and accumulates there rather than in the body, but is essentially well aerated.

The symptomatology of ruptured aneurysm of the right anterior aortic sinus of Valsalva, leading to communication between the aorta and the base of the right ventricle as given by Abbott, shows many points of similarity, including dyspnea without cyanosis, precordial vibration and thrill of intense purring character, loud sawing murmur, etc. This condition as well as pure ventricular rupture may be differentiated from patent ductus by the extremely superficial character relative to the chest wall and by the location and intensity of the sounds. A history of marked pulsation in the temples and vessels of the neck, dyspnea on exertion without cyanosis or edema, precordial vibration and a strong diastolic thrill over the precordium, a systolic thrill in vessels of the neck, a loud rough diastolic murmur at the base with systolic and diastolic murmur at the apex as in Abbott's case may indicate that the patient is suffering from a ruptured aneurysm of the right anterior sinus of Valsalva, especially if the patient is relatively young. Such a condition may be compatible with life for years. This is not so with ruptured interventricular septum which is always a terminal process and occurs in old age.

The symptomatology of other cases of cardiac rupture is quite different. Where the rupture is into the pericardium, the patient is seen to fall over dead or is found dead. If the patient survives for a short time, the symptoms are those of acute collapse with pallor, air hunger, marked cyanosis, stertorous breathing, cold sweat and sometimes convulsions or unconsciousness. Prior to the rupture the patient may have had cough, dyspnea, vertigo, syncope, hematemesis, anginal pain, diarrhea, vomiting, etc., namely, the signs of coronary disease.

#### SUMMARY AND CONCLUSIONS

1. Two cases of perforation of the interventricular septum following coronary thrombosis are reported.

2. This rare condition should be suspected when there is superimposed upon the picture of coronary occlusion a striking symptom complex consisting of (a) progressive harsh systolic murmur and thrill over the precordium, (b) gradual extinction of the aortic second sound, and (c) marked disproportion between the force of cardiac action and the strength of the pulse.



3. The mechanism seems plainly indicated. The septal perforation permits passage of blood from the stronger left ventricle to the weaker right through a gap with rough edges reducing the stream that passes the normal aortic opening into the general circulation. Death may take place from pulmonary congestion and edema before the opening is large enough to divert sufficient blood from the systemic circulation to cause disappearance of the pulse.

4. The condition may be distinguished from congenital malformation by the age and previous condition of the patient as well as the shorter survival period.

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## THE BLOOD PRESSURE AND ELECTROCARDIOGRAM IN EXPERIMENTAL PERICARDIAL EFFUSION\*

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A VERY detailed account of the blood pressure changes in dogs during experimental pericardial effusion was given by Cohnheim in his "Lectures on General Pathology."<sup>1</sup> Oil was injected into the pericardial sacs of medium sized dogs and the pressure produced measured by an oil manometer. Kymographic tracings of the blood pressure in the femoral and pulmonary arteries were made with mercury manometers, while the venous pressure was recorded by a sodium carbonate manometer attached to the external jugular vein. The concentration of sodium carbonate solution used was not stated. Cohnheim found that an intrapericardial pressure of 30 to 40 mm. of oil caused a slight rise in venous pressure. An oil pressure of 60 to 70 mm. produced a fall of 20 to 30 mm. Hg in the arterial pressures and a rise of venous pressure to about 60 mm. of sodium carbonate solution. When the intrapericardial pressure reached 100 to 120 mm. of oil, the pulmonary and femoral pressures fell to about one-half of their original values, and the respiratory and systolic fluctuations of the mercury manometers were decidedly damped. The venous pressure rose to about 100 mm. of sodium carbonate solution. Further increase of pressure in the pericardium reduced the arterial pressure almost to zero, the pulse pressure disappearing first in the pulmonary and a little later in the femoral artery. The jugular pressure increased greatly. Usually an oil pressure of about 240 mm. was sufficient to reduce the pressure in the pulmonary artery to a minimum, while the femoral tracings still showed slight pulsations. The manometer in the external jugular vein then recorded more than 220 mm. of sodium carbonate solution. This condition of minimal arterial pressure could be maintained for two to three minutes without causing serious cardiac damage. On reducing the intrapericardial pressure the pulse appeared first in the pulmonary artery. The pulse waves were at first large and infrequent but soon returned to normal size. The arterial pressures rose rapidly to their normal values and usually slightly higher, while the venous pressure fell to zero. Cohnheim noted that if an increased intrapericardial pressure were maintained for a few minutes there was a gradual stretching of the pericardium which, of course, led to a diminution of the pressure in the pericardial sac and to a slight rise in arterial and fall in venous pressure.

Recently Scott, Feil and Katz<sup>2</sup> reported a case of hemopericardium and another of purulent pericarditis in which changes occurred in the electrocardiogram similar to those observed in recent myocardial in-

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farection, and in animal experiments they produced similar electrocardiographic changes by artificial pericardial effusions.<sup>3</sup>

At the suggestion of Professor Roger S. Morris we sought more complete records of the relationship between intrapericardial and arterial pressures and the electrocardiogram to determine, if possible, how great a pressure in the pericardial sac is necessary to cause obvious changes in the T-wave of the electrocardiogram.

Medium sized dogs were given hypodermic injections of  $\frac{1}{2}$  to  $\frac{2}{3}$  grain morphine sulphate and anesthetized with ether. A tracheal cannula was inserted for control of the anesthetic. The pressure in the right carotid artery was recorded by a mercury manometer. The chest was opened and artificial respiration established. The intrapericardial pressure was varied by introduction of saline through a suitable cannula and measured by a mercury manometer. Injection of drugs was made from burettes attached to cannulas in the femoral veins. Electrocardiographic tracings were recorded in Lead II, using the Victor apparatus. The times of taking these records were marked on the kymograph by an electromagnetic signal. Throughout these experiments the chest was kept open. The thoracic organs were protected from drying by a layer of paraffin.

Our kymographic records completely confirmed the data of Cohnheim. A gradual increase in the intrapericardial pressure caused a fall in carotid pressure. The pulse pressure diminished and finally the carotid pressure tracing became a straight line parallel to and almost touching the base line. If the increases in the intrapericardial pressure were made by stages, there were established definite levels of arterial pressure for each stage. These were maintained usually for a minute or more, but then a slight rise in blood pressure was caused by stretching of the pericardium. When the intrapericardial pressure was slowly but continuously increased, there appeared to be a definite mathematical relationship between the pressure in the pericardial sac and that in the carotid artery, which was expressed by the general formula

$$P_x = \frac{P_o}{m.e (ax + bx^2 + cx^3 + dx^4)}$$

in which

$P_o$  is the initial blood pressure (mean of systolic and diastolic pressures) in mm. Hg,

$P_x$  is the mean blood pressure under an intrapericardial pressure of

$x$  mm. Hg, and

$a, b, c, d$  are constants for the particular experiment.

The observed and calculated blood pressures in a typical experiment are given in Table I. For this series  $P_o = 92$ ;  $m = 0.9828$ ;  $a = +0.02321$ ;  $b = -0.00737$ ;  $c = +0.00135$ ;  $d = -0.000015$ .

With a decrease in intrapericardial pressure there was not an immediate response in blood pressure if this had been reduced to a mini-

TABLE I

| INTRAPERICARDIAL PRESSURE |  | MEAN CAROTID ARTERIAL PRESSURE |       |
|---------------------------|--|--------------------------------|-------|
| MM. HG                    |  | MM. HG                         |       |
|                           |  | OBS.                           | CALC. |
| 2                         |  | 91                             | 91.8  |
| 4                         |  | 90                             | 88.2  |
| 6                         |  | 83                             | 83.0  |
| 8                         |  | 70                             | 71.9  |
| 10                        |  | 57                             | 56.7  |
| 12                        |  | 40                             | 40.9  |
| 14                        |  | 27                             | 27.1  |
| 16                        |  | 17                             | 16.6  |
| 18                        |  | 10                             | 10.1  |
| 20                        |  | 6                              | 5.3   |

mum. After a short pause the heart began to beat forcefully and usually in such a way as to produce violent oscillations in the carotid pressure tracing and sometimes also in the tracing of the intrapericardial pressure. The pulse became more rapid, arterial and pulse pressures increased, and soon the heart was restored to normal activity. Fig. 1 shows the whole cycle of pressure changes, while Fig. 2 is an example of the more violent oscillations in the blood pressure tracing on reduction of pressure in the pericardial sac.

These changes in the intrapericardial pressure could be repeated many times on the same animal without any appreciable change in the myocardium but with a gradual stretching of the pericardium. This stretching was indicated by the increasing volume of fluid which must flow into the pericardial sac to produce a given intrapericardial pressure.

The actual volumes of saline introduced into the pericardial sac were not usually recorded, but data from a typical experiment are shown in Table II. It will be seen, as noted by Katz and Gauchat,<sup>4</sup> that there is not a simple arithmetic ratio between the volume of the fluid introduced and the pressure caused by this fluid. The actual relationship between volume and pressure is expressed by the exponential formula

$$P = e^{aV}$$

For the calculated data of Table II the value of  $a$  was 0.0165.

TABLE II

| C.C. SALINE INJECTED | MEAN CAROTID PRESSURE<br>MM. HG | INTRAPERICARDIAL PRESSURE |       |
|----------------------|---------------------------------|---------------------------|-------|
|                      |                                 | OBS.                      | CALC. |
| 0                    | 96                              | 0.0                       | 0.0   |
| 25                   | 95                              | 1.5                       | 1.5   |
| 50                   | 90                              | 2.5                       | 2.3   |
| 75                   | 78                              | 4.0                       | 3.5   |
| 100                  | 64                              | 5.5                       | 5.2   |
| 125                  | 28                              | 8.0                       | 7.9   |
| 150                  | 10                              | 12.0                      | 11.9  |
| 175                  | 2                               | 18.0                      | 18.0  |

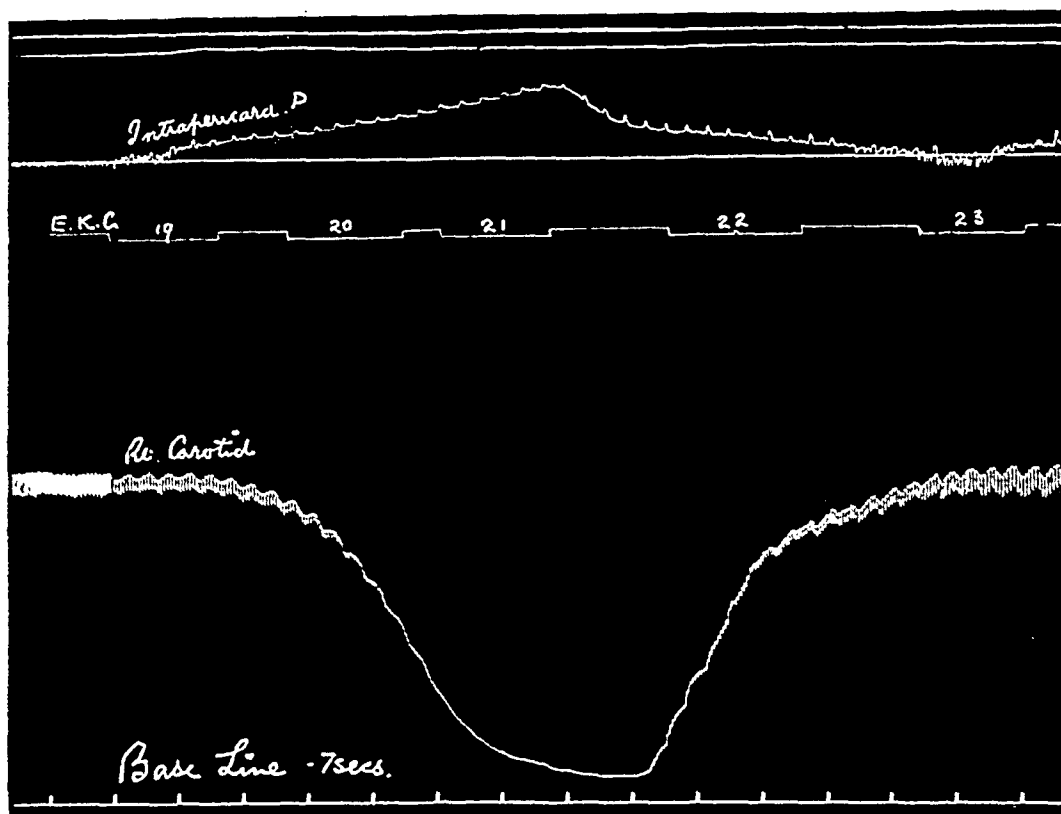


Fig. 1.—The influence of intrapericardial pressure upon blood pressure.

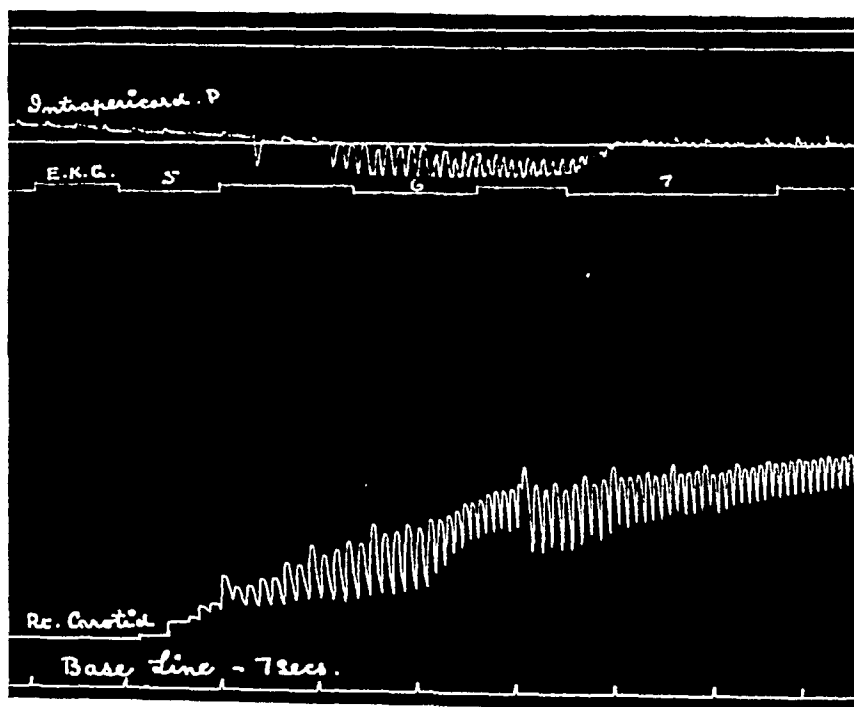


Fig. 2.—Recovery from increased intrapericardial pressure. Note the large pulsations in the carotid artery.

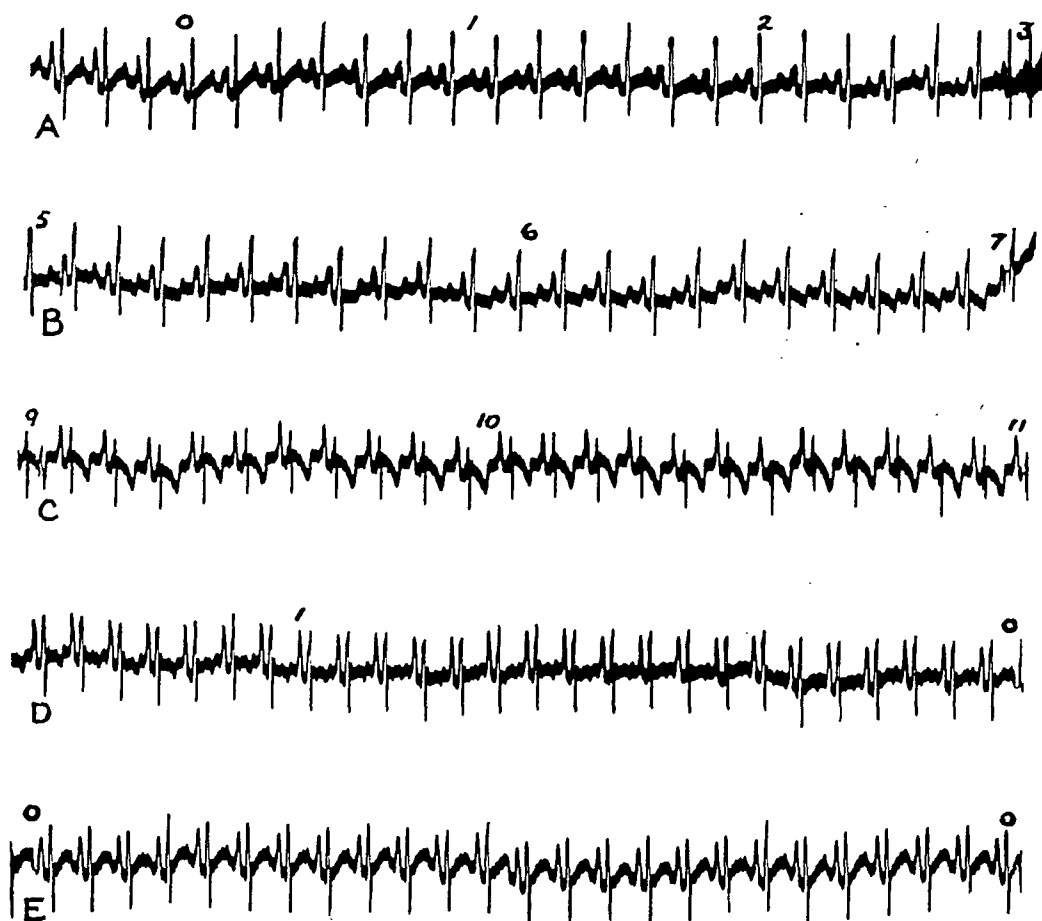


Fig. 3.—The electrocardiogram during changes in intrapericardial pressure. *A, B, C* during increasing pressure. Note the gradual inversion of the T-waves. *D, E* during recovery on release of pressure. The numerals indicate the intrapericardial pressure in millimeters Hg.

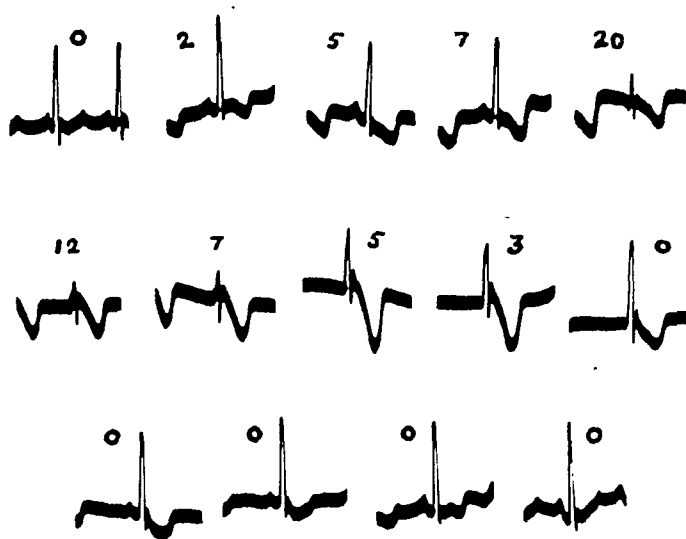


Fig. 4.—Striking examples of QRS segments and T-waves during changes in intrapericardial pressure. The numerals indicate pressure in millimeters Hg. The last 8 examples were obtained during times marked 5 to 7 on Fig. 2.

The intrapericardial pressure necessary to produce a minimal blood pressure varied in our experiments from 15 to 19 mm. Hg. Cohnheim does not mention the specific gravity of the oil used in his pericardial manometer, but assuming it to have a value of 0.90 to 0.95 the pressure of 240 mm. oil which he usually found adequate to reduce the pulmonary arterial pressure to a minimum would correspond to from 15.8 to 17.0 mm. Hg.

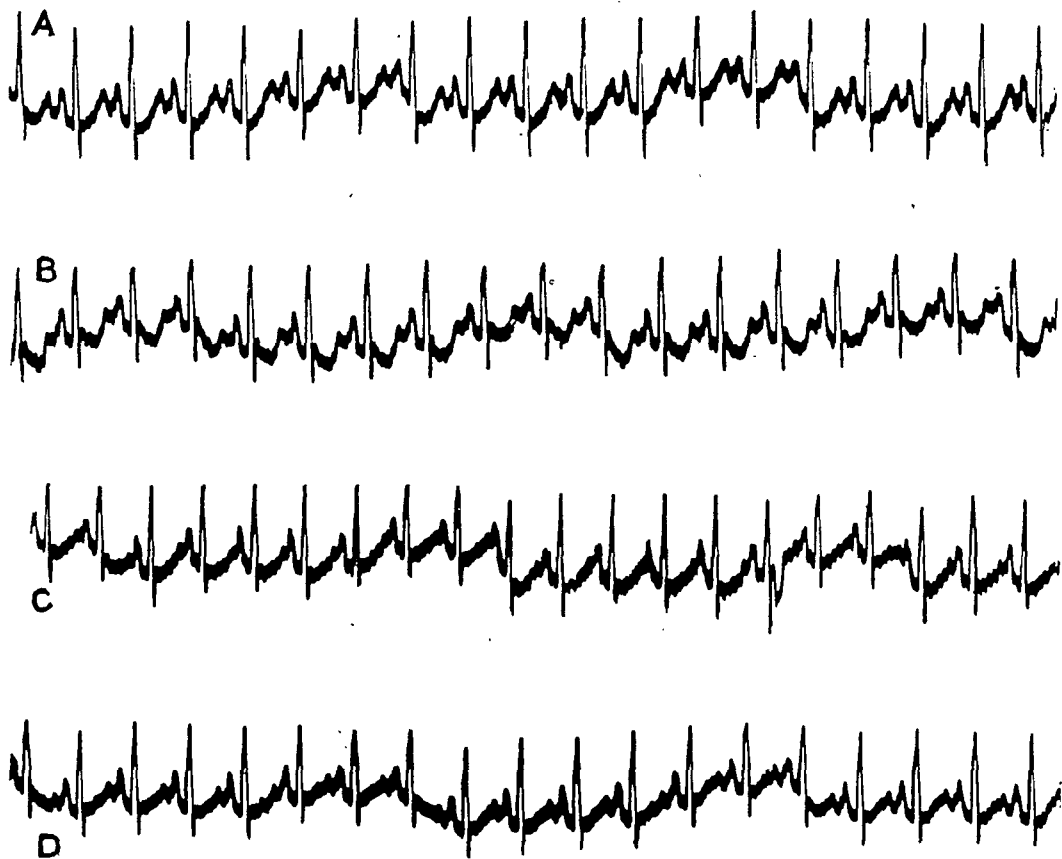


Fig. 5.—The influence of adrenalin on the electrocardiogram in increased intrapericardial pressure. *A* is a control. *B* shows inversion of T-waves by a pressure of 4 mm. Hg in the pericardial sac. *C* is a record taken six seconds after injecting 1 c.c. of 1:10,000 adrenalin solution into the femoral vein. The arterial pressure was beginning to rise at the commencement of this record. Note the restoration to positive T-waves. *D* was taken thirty-five seconds after the injection of adrenalin. The pressor effect of the drug had worn off.

The changes in the electrocardiogram during increased intrapericardial pressure and during recovery on release of pressure are shown in Figs. 3 and 4. Fig. 3 is an almost continuous record of one experiment. Fig. 4 shows stages in production of coronary T-waves. This figure is constructed from records of the same experiment as is shown partly in Fig. 2, the last 8 tracings being from electrocardiographic records taken during times marked 5, 6 and 7 on that figure.

These changes in the electrocardiogram are similar to those recorded by Scott, Feil and Katz. The most marked features are the diminution in voltage of the QRS segments and the gradual inversion of the T-wave with production of the coronary type. During recovery on release of

pressure there was a gradual return to normal, but usually in the early stages of recovery the QRS segments were of greater than normal voltage, and there was an increase in ventricular rate.

By correlation of electrocardiographic with kymograph tracings it was found that a definite change in the T-wave toward negativity was always produced by an intrapericardial pressure of from 3 to 8 mm. Hg.

It appeared of interest to examine the influence upon the electrocardiogram of pressor drugs injected while the intrapericardial pressure was increased. Adrenalin (1 c.c. of 1 in 10,000 solution) showed the typical blood pressure rise if the intrapericardial pressure were not too high. There was sometimes, but not always, a corresponding rise in the intrapericardial pressure. Adrenalin restored the T-waves to their normal positivity, this effect commencing even before the rise in arterial pressure and continuing after the pressor effect of the drug had disappeared (Fig. 5). This result was still shown when the rise in arterial pressure caused an increase in intrapericardial pressure. If, however, the pressure in the pericardial sac were sufficiently high at the time of injection of adrenalin, there was no rise in blood pressure and the changes in T-waves were absent. But the blood pressure rose in the usual fashion immediately the intrapericardial pressure was released. If the pressure in the pericardial sac were sufficient to produce a minimal arterial pressure at the time of injection of adrenalin, then, on release of this intrapericardial pressure, the heart beat very irregularly. The intravenous injection of 2 c.c. of a 0.5 per cent solution of ephedrine sulphate while the intrapericardial pressure was raised produced the same changes as did adrenalin. And once more the pressor effect was absent if the intrapericardial pressure were too high and appeared immediately this pressure was released. A large pericardial effusion obviously greatly hinders circulation.

In applying to clinical studies the results of such experiments as are recorded above, it is important to consider the factor of time. In the laboratory one can only observe the influence of acute pericardial effusions upon blood pressure and the electrocardiogram. In clinical practice one meets more often with effusions slowly accumulating. Even in the laboratory one observes a gradual relaxation of the pericardium sufficient to compensate for the acutely produced intrapericardial pressure. This is especially the case when the pressure produced is of that order just sufficient to cause a reversal of T-waves, viz., a pressure of 3 to 8 mm. Hg. Unless such a pressure be maintained by increasing the volume of the injected fluid, it will be spontaneously and rather rapidly diminished by stretching of the pericardium and the electrocardiogram will revert to normal. It is understandable, therefore, that single, isolated observations of blood pressure and the electrocardiogram in clinical cases will often fail to show the abnormalities which have been produced in our experiments. When such abnormalities are observed clinically, then one may conclude either that the pericardial effusion is of very recent forma-



tion or that it is of such a volume as to have extended to the limit the power of relaxation of the pericardium and this volume of effusion must be greater than would be necessary, in the laboratory, to produce equivalent changes in blood pressure and cardiac activity.

Pyopericardium is uncommon clinically. Yet the rapid accumulation of a purulent exudate in the pericardium may reproduce the conditions of our experiments, as in the case reported by Harvey and Scott.<sup>5</sup> The coronary type of T-wave, associated with pain, fever, lowered blood pressure and leucocytosis, is most often seen in cases of coronary occlusion. Unless the physical signs of pericardial effusion are clear or suggestive, the differential diagnosis may be difficult or impossible. X-ray films of the chest may aid in the differentiation.

#### SUMMARY

1. The increase in intrapericardial pressure caused by an acute pericardial effusion produces a fall in arterial blood pressure.

2. If the intrapericardial pressure be increased by stages, there is a definite blood pressure established for each stage. This blood pressure is maintained for a minute or more, but there finally occurs a stretching of the pericardium which tends to restore normal conditions.

3. If the intrapericardial pressure be slowly and continuously increased, there is a definite mathematical relationship between the pressure in the pericardial sac and the arterial blood pressure.

4. During an increase in the intrapericardial pressure there occur changes in the electrocardiogram, as described by Katz, Feil and Scott, consisting chiefly of a gradual diminution in the voltage of the QRS segments and development of and increase in negativity of the T-waves, this latter change extending even to the production of T-waves of the coronary type.

5. An intrapericardial pressure of 3 to 8 mm. Hg is sufficient to produce an obviously negative T-wave.

6. When the intrapericardial pressure is sufficiently high to produce negative T-waves, the intravenous injection of adrenalin or ephedrine sulphate solutions will restore the electrocardiogram to normal. This change commences before the pressor effect of the drugs is evident on a carotid pressure tracing and persists after that effect has worn off. It is shown also even if the rise in arterial pressure is accompanied by a rise in intrapericardial pressure.

7. If the intrapericardial pressure be sufficiently high, the circulation is hindered to such an extent that neither adrenalin nor ephedrine will cause a rise in arterial pressure. But this rise occurs immediately on re-rise in intrapericardial pressure.

8. The negative T-wave may resemble in all respects that seen in coronary occlusion. Since the rapid accumulation of a purulent exudate in the pericardium may be accompanied by intense pain, lowering of the

blood pressure, fever and leucocytosis, suggesting coronary occlusion, the presence of a coronary T-wave in such a case may offer great diagnostic difficulties.

The authors wish to express their sincere thanks to Dr. R. S. Morris for his continuous and encouraging interest in this work.

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## PARTIAL BUNDLE-BRANCH BLOCK\*†

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ATTENTION has been called recently to the occurrence of transient bundle-branch block of various types,<sup>1-14</sup> which usually takes the form of a 2:1 partial bundle-branch block. In the cases reported there have been included cases of alternation between right and left bundle-branch block. Transient bundle-branch block has been assumed to occur as the result of functional disturbances in the conduction paths, the cause of which has been ascribed to various factors. An unusual case of partial bundle-branch block of one bundle associated with bundle-branch block of the opposite bundle (at times leading to alternation) and incomplete A-V block of first and second degrees, is presented because it throws light on a mechanism which can produce partial bundle-branch block.

### CASE REPORT (SUMMARY)

Dinah P., housewife, aged sixty-five years, was admitted to the hospital on Jan. 3, 1931, complaining of an attack of dizziness and faintness. She noticed these attacks for the first time about three weeks previously. These attacks came on at work with only moderate exertion, lasted several minutes, and became as frequent as three a day before admission.

She had been under medical management for peptic ulcer for the past five years; otherwise her past history is irrelevant.

On physical examination the patient appeared aged, undernourished and was lying comfortably in bed. She had an arcus senilis and bilateral nuclear cataracts. The lungs were clear throughout. The heart was but slightly enlarged to the left, and its sounds were distant and muffled. A presystolic gallop rhythm was present. The aortic second sound was accentuated and louder than the pulmonic second. The pulse rate was 64 and grossly irregular.

The patient was kept in the hospital until Feb. 27, 1931, during which time various therapeutic procedures were tried, as follows:

1. Oxygen tent, Jan. 6 to Jan. 12.
2. Atropine sulphate gr. 1/50 hypodermically (a) Jan. 23, (b) Feb. 4.
3. Camphor in oil hypodermically, 1 c.c., Jan. 28.
4. Caffeine benzoate hypodermically, 7½ gr., Feb. 1.
5. Adrenalin, 1 c.c. of 1/1000 solution hypodermically (a) Jan. 27 (b) Feb. 25.
6. Glucose, 50 c.c. of a 50 per cent solution intravenously, and insulin, 25 units intramuscularly (a) Feb. 18, glucose given first; (b) Feb. 3, insulin given first.
7. High carbohydrate diet, as tolerated, consisting of protein 50 gm., fats 80 gm., carbohydrates 250 gm. Feb. 7 to Feb. 27.

Laboratory Data.—Wassermann reaction was negative. Blood sugar ranged from 76 to 86 mg.; blood nonprotein nitrogen ranged from 38 to 58; blood creatinine ranged from 1.7 to 2.0; and blood cholesterol ranged from 227 to 231. On Jan. 5,

\*From the Heart Station and Medical Clinics, Michael Reese Hospital, Chicago.  
†Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

the red blood cells were 4,240,000, hemoglobin 70 per cent; her blood pressure varied from 130/65 to 158/65; and the urine and stools were negative on repeated examination.

The diagnosis on discharge was arteriosclerotic heart disease, Stokes-Adams syndrome and chronic atrophic emphysema.

### DISCUSSION

The various therapeutic regimes were without apparent effect on the cardiac mechanism except in the case of atropine and adrenalin. Atropine produced an acceleration in sinus rate and adrenalin tended

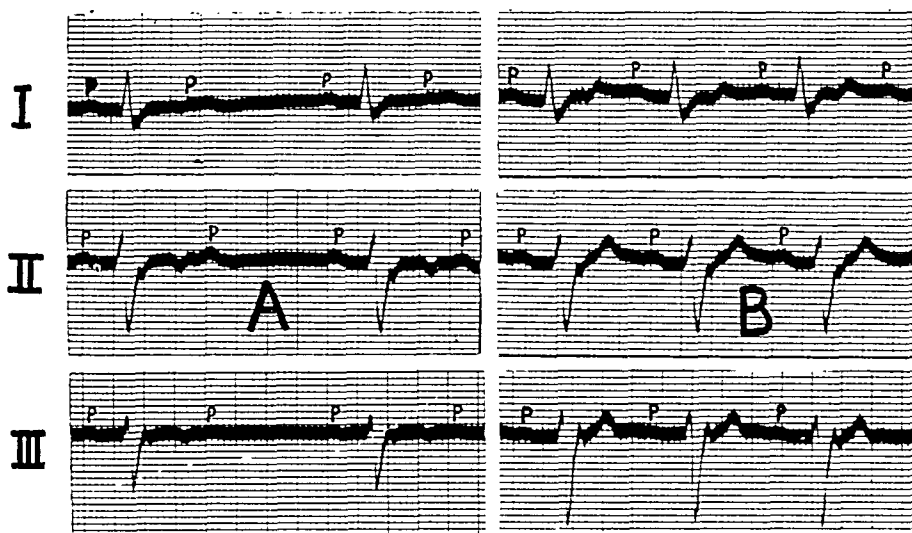


Fig. 1.—Shows the effect of adrenalin on the A-V block. Segment A, taken before adrenalin was given, shows 2:1 A-V block with a P-R interval in the conducted beat prolonged and a single type of bundle-branch block, the dominant type. Segments B and C were taken after the administration of 1 c.c. of 1/1000 adrenalin hypodermically. In segment B there is 1:1 conduction with prolonged P-R interval. Note the large, upright T-waves in all leads. In segment C there are occasional dropped beats and typical Wenckebach periods. Note that the T-waves are smaller in this segment. In this figure the P-waves are labelled.

to improve the A-V conduction and altered the ventricular deflections by increasing the amplitude of the T-wave. In Fig. 1A is shown the change from a 2:1 A-V block before adrenalin (segment A) with P-R of 0.26 sec. to a 1:1 conduction with P-R of 0.28 sec. in segment B during adrenalin; after the maximum effect of adrenalin had worn off there appeared frequent dropped beats and Wenckebach periods (segment C). These changes in A-V block occurred without any alteration in sinus rate. The intraventricular block in this illustration is of the predominant type seen in this patient and according to classical terminology would be called a right bundle-branch block.\* The changes in T-wave following adrenalin are clearly seen.

TABLE I

| A-V BLOCK                                     | BUNDLE-BRANCH BLOCK<br>(CLASSICAL TERMINOLOGY) | SINUS RATE  | AVERAGE     |
|---|--|---|-------------|
| Prolonged P-R                                 | right  | 54, 55, 56, 56, 58, 58<br>60, 62, 62, 65*, 65*, 67*<br>71*, 71*, 72*, 72* | 63<br>(57)† |
| Prolonged P-R,<br>occasional dropped<br>beats | right  | 68, 68, 68<br>72, 73, 75  | 71          |
| Prolonged P-R,<br>dropped beats               | right<br>and<br>left‡                          | 55<br>60, 62, 66, 68<br>72, 75, 75*, 77                                   | 69          |
| Prolonged P-R,<br>dropped beats               | right<br>and<br>left§                          | 60, 62, 67, 68, 68, 68<br>72, 75, 75, 75, 75, 79, 79, 79<br>81, 83, 88    | 74          |
| 2:1   | right  | 72, 75, 76, 79<br>81, 86<br>94<br>107, 107                                | 84          |

\*During adrenalin experiment.

†Average of rate omitting adrenalin experiment.

‡"Right" type of complexes occur in some of conducted impulses without previous beat being dropped.

§"Right" type of complexes occur only after previous dropped beat.

An analysis of the 61 sets of curves taken on this patient showed that, considering the variety of conditions under which these records were taken, a correlation could be made between the mechanism and the sinus rate. There were of course other influences besides heart rate which affected the conduction of the impulse through the ventricles as the experiment with adrenalin cited above demonstrated. The presence of a sinus arrhythmia and occasional nodal extrasystoles (viz., Lead III, Fig. 2B) further complicated the situation. The data of this correlation are assembled in Table I. At the slower and the faster rates only the so-called right bundle-branch block was present, in the former with 1:1 and in the latter with 2:1 A-V conduction. In the intermediate range of sinus rates the block was less regular, Wenckebach periods occurred and there were frequent dropped beats. In this sinus rate range an

\*The classical terminology will be followed in this report.

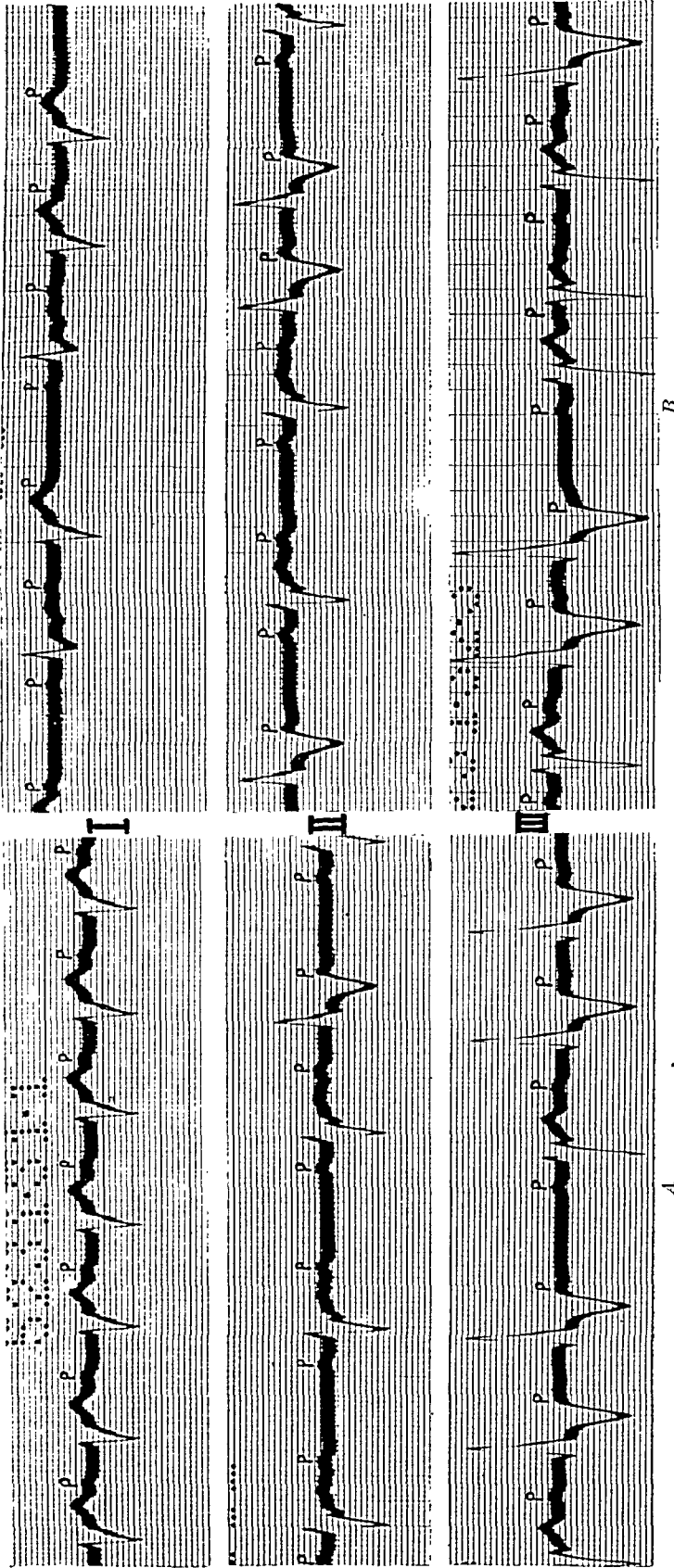


Fig. 2.—A. In Lead I is shown 1:1 conduction with prolonged P-R intervals and a persistent bundle-branch block of the uncommon type in this patient. In Lead II there are frequent dropped beats giving rise to 2:1 and 3:2 block. The second ventricular complex of the 3:2 block is of the type shown in Lead I; the rest are of the opposite type. In Lead III all but two are of the same type of bundle-branch block as in Lead I. In B the presence of a partial bundle-branch block is shown. The contrast in configuration of the two types of ventricular complexes is clearly seen. In Lead III there is a nodal extrasystole the ventricular complex of which has the configuration of the dominant type of bundle-branch block. The P-waves in this illustration are labelled.

interesting phenomenon appeared, viz., transient block of the other bundle branch (the left). The change in block from right to left occurred at times for a number of successive beats as in Lead I of Fig. 2A, on the one hand, and for an occasional beat, as in Lead II of Fig. 2A, on the other. Other combinations were seen, viz., 4:3 block with the right type after the blocked auricular impulse, the left in the others, as in Lead III of Fig. 2A; and 3:2 block as in Fig. 3A with an alternation of the type of bundle-branch block between right and left, the former occurring after the blocked auricular impulse. Irregular types such as shown in Fig. 2B and 3B were also observed often. Wenckebach periods with progressive lengthening of P-R occurred when the transient left bundle-branch block was present, just as was the case when the right bundle-branch block was present (compare Lead III of Fig. 2A, all leads of Fig. 2B, and Fig. 3B with all leads of Fig. 1B). In fact the progressive lengthening of P-R was equivalent in the two types of bundle-branch block as can be seen by comparing the P-R intervals of the

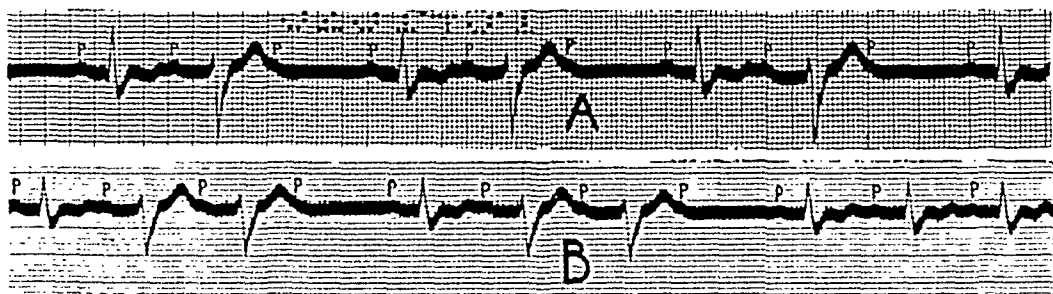


Fig. 3.—Segment A shows an alternans between the two types of bundle-branch block, associated with a 3:2 A-V block. Segment B shows in a single lead the appearance of 1:1 conduction of the two types of bundle-branch block. The P-waves in this illustration are so labelled.

last three ventricular complexes of Fig. 3B with the first three or middle three.

There can be no question that the severity of the A-V block was dependent on the sinus rate; the block increasing, with some variation, from a simple prolongation of the P-R interval to a 2:1 conduction. The administration of adrenalin was the only procedure with noticeably altered this relationship by improving A-V conduction without changing the sinus rate. The other therapeutic procedures either had no apparent effect or acted by changing the sinus rate, as in the case of atropine.

The occurrence of a transient left bundle-branch block was limited to the intermediate sinus rate range (see Table I). In no instance did this transient left block occur after a dropped beat. In other words, it always occurred after at least one previous conducted impulse. The following explanation is offered to account for this peculiar phenomenon:

There is in this case a permanent organic damage in the right bundle branch and in the A-V junctional pathway. The block in this bundle branch is unaffected by changes in heart rate in the range studied; that of the A-V junctional tissue varies with the sinus rate. The block

in the left bundle is more extensive than in the right but is not permanent. If sufficient time is allowed for recovery after the passage of an impulse, before the following impulse reaches it, the impulse will pass without any appreciable delay. If, however, the second impulse comes earlier, it is completely blocked; that is to say, it reaches the left ventricle by a circuitous route. Of course, the impulse is delayed to both ventricles under these circumstances but reaches the right sooner than the left. Since the QRS complex is not registered until some of the ventricle is activated, the delay of the impulse in reaching the right ventricle can only prolong the P-R slightly; and since the right is activated before the left ventricle, the complex will take on the appearance of left bundle-branch block.

#### SUMMARY

A case is reported in which there is a combination of a region of permanent and complete block of one bundle branch associated with less complete but more extensive block in the other bundle, and complicated by the presence of incomplete block of the A-V junction. The presence of this combination with changing ventricular rate caused the appearance of transient bundle-branch block of one type to be superimposed on that of the opposite type, with, at times, an alternation between the two.

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## POSSIBLE INTRANODAL BLOCK. A REPORT OF CASES\*

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THIS report is concerned with electrocardiograms from three cases showing rhythmic deflections at a regular rate, unrelated to the normal auriculo-ventricular complexes.

In one case these deflections are identical in form with the P-waves of the auriculo-ventricular complexes. The latter complexes have normal P-R intervals. The electrocardiogram from this case gives the impression of a double auricular rhythm, that is, of two sets of auricular contractions, both rhythmical, but unrelated to each other. The extra rhythm in the other two cases does not appear so evidently auricular in origin, but some features are suggestive.

### CASE REPORTS

CASE 1. J. K., Unit No. 25076, a white male twenty-two years old, was admitted to the hospital because of acute rheumatic fever. The onset was sudden with stiffness, pain and swelling of both ankles together with fever and sweating. The patient had noted these symptoms six weeks prior to entrance upon waking from a nap taken in his automobile on a rainy day. The symptoms had diminished somewhat at the time of entrance. Anorexia had been present for the first three weeks, and during the six weeks the patient had lost twenty pounds in weight. Otherwise the history was insignificant.

Physical examination showed the pharynx to be injected, the left tonsil large, cryptic and moderately injected. The anterior cervical chain of glands was palpable on both sides, but the glands were larger on the left (almond size). Swelling and redness in the region of the malleoli were present in both ankles. The skin was damp and cold. Otherwise the examination was negative.

The temperature was 101.6° F. rectally, the pulse rate was 90 per minute. The leucocyte count was 16,000 per c.mm. The red blood count and hemoglobin were normal. The Wassermann and Kahn tests were negative. The urine was normal.

Within six days after admission the temperature was normal, the excessive perspiration had stopped, and the swelling and pain in the joints were less, although during that time he had complained of pain and stiffness in the right shoulder and fingers, and in the lumbar region at times. On two or three occasions a soft apical systolic murmur was heard, but this was not constant. Electrocardiograms were taken on the tenth and eleventh days of hospitalization. On the fourteenth day the symptoms had disappeared and the patient left the hospital against advice.

In Lead I of the first electrocardiogram, (Fig. 1A) the peculiar appearance of two independent sets of auricular waves is seen. This finding was not present in the tracing taken the following day.

It is quite evident that in this case there is no noticeable difference in the form of the auricular waves preceding the ventricular complexes and the waves of the other set. This other set is rhythmic, we think, although

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some of the waves are not evident because of coincident ventricular complexes. The intervals between the waves vary from 0.42 to 0.56 seconds with an average rate of 113 per minute. The auriculo-ventricular complexes occur at an average rate of 85 per minute. The curve shows a slight sinus arrhythmia, and both sets of waves vary practically together but not to the same extent. This relation, together with the similarity in form of the regular auricular waves and the waves of the other set, makes it probable that they are both cardiac in origin.

CASE 2. L. M., Unit No. 382, a Jewish girl nine years old, has been under observation from time to time for the past three years. Prior to admission here the only past history of importance was scarlatina at the age of six, uncomplicated. There is a family history of syphilis.



Fig. 1.—Short sections of electrocardiograms from the cases with abnormal rhythmic deflections. A, Lead I from Case 1. The abnormal waves are indicated by arrows. B, Lead I from Case 2. C, Lead III from Case 2. D, Lead II from Case 3.

Although she was examined several times during these three years, nothing referable to the cardiovascular system worthy of note was discovered until June of 1931, with the possible exception of an attack of acute tonsillitis, for which tonsillectomy was finally performed in June of 1930.

In June of 1931 she was hospitalized because of a gastrointestinal upset with slight temperature, nausea, vomiting and generalized abdominal pain which persisted for five or six days. The leucocyte count rose as high as 15,500, with 75 per cent polymorphonuclears. The gastrointestinal symptoms, temperature and leucocytosis subsided entirely, but shortly before discharge a duplication of the first heart sound at the apex was noted. The blood pressure was 106 mm. of mercury systolic and 76 mm. diastolic in the sitting position. In the supine position the systolic pressure was 102 mm., and the diastolic pressure could not be read, the sharp sounds persisting to the zero mark. Marked sinus arrhythmia was present.

An electrocardiogram was taken, Leads I and III of which are shown in Fig. 1 B and C. From that time until the present the patient has been followed and six electrocardiograms have been taken, without any reappearance of the peculiar de-

deflections of the first tracing. The heart findings remain the same except that recently there has been a loud musical murmur, best heard in the second interspace to the right of the sternum, at times to-and-fro, and at times limited to diastole. This murmur is present only when the patient is in the upright position, disappearing entirely when she lies down. The blood pressure readings remain the same.

The electrocardiogram from this patient shows deflections in Leads I and III similar to those in Lead I of the first case in that they vary in rate with the variations in rate of the normal complexes due to sinus arrhythmia but not to the same extent. The form of the waves, however, is markedly different from that of the P-waves preceding the ventricular complexes.

CASE 3. J. C., Unit No. 31513, a white male twenty-five years old, with chronic glomerulonephritis, hypertension, hypertensive neuroretinitis and right facial paresis showed the electrocardiographic manifestations in question (Fig. 1 *D*) about a week before his death while he was suffering from myocardial insufficiency and uremia, although several previous and one subsequent tracing furnished no further evidence of this abnormality.

In this case Lead II shows rhythmic deflections at a slow rate, which is slightly variable. The interval varies from 1.25 to 1.45 seconds with an average rate of 42 per minute. The rate of the usual auriculo-ventricular complexes is absolutely regular at 92 per minute.

The identity of these rhythmic deflections as evidences of auricular activity in Cases 2 and 3 is not so apparent as in Case 1.

#### DISCUSSION

Without the first case the other two might not be of sufficient interest to merit special consideration, although it would be difficult to explain the abnormal waves as artefacts. Artefacts might possibly occur rhythmically, as the result of the rhythmic contraction of some extracardiac muscle, but it is difficult to conceive of an extracardiac rhythm variable with the variability in heart rate due to sinus arrhythmia. We believe that these waves are manifestations of cardiac activity, at least in Case 1.

Case 1 has one peculiarity, not shared by the others, that makes it seem even more likely that the waves are of auricular origin; namely, that the abnormal waves are identical in form with the P-waves of the normal complexes. In this case, as in the others, the waves are rhythmic and the rhythm varies with the sinus arrhythmia of the heart.

Fig. 2 *A* shows the rates of the two rhythms plotted from Case 1. It will be noted that in general the intervals between the normal complexes and the intervals between the abnormal waves lengthen and shorten simultaneously. Fig. 2 *B* and *C*, shows similar graphs constructed from the curves from Case 2. No graph from Case 3 is shown because, although the rhythm of the abnormal waves is slightly variable suggesting a sinus arrhythmia, the rate of the normal complexes is absolutely regular. This makes it impossible to determine whether the variations in rate are synchronous with respiration or not.

The abnormal waves occur in very close proximity to normal auricular waves in some instances, and very soon after the ventricular complexes in others (see the second ventricular deflection in Fig. 1 A). They are present so soon after the ventricular complexes that the muscle whose stimulation gave rise to the ventricular complex must still be in a refractory phase. Since the QRS complexes are normal in appearance, it is extremely likely that all the ventricular muscle is stimulated and contracts at the time of the ventricular complex. If this is true the abnormal waves cannot be the result of ventricular activity. The same argument applies in the case of the auricular waves except that the auricular complex is not so characteristic as the QRST, and it would be difficult to determine whether all the auricular muscle was stimulated at the time

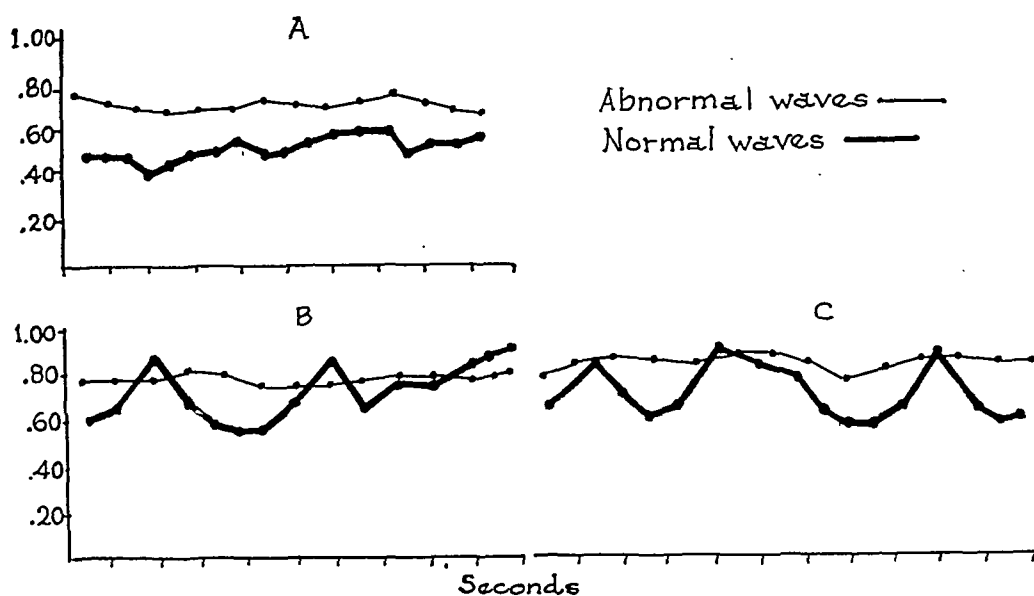


Fig. 2.—Graphs constructed from the electrocardiograms of Cases 1 and 2. The vertical distance represents the time in seconds between the P-waves of the normal complexes (heavy line) and between the abnormal waves (light line). The horizontal distance represents absolute time in seconds. A, Lead I from Case 1. B, Lead I from Case 2. C, Lead III from Case 2.

of the P-wave. It is possible, therefore, that the normal P-waves and the abnormal waves are the electrocardiographic expressions of the activity of separate portions of the auricular muscle.

This view is supported further by the fact that the abnormal waves are subject to the influences that cause sinus arrhythmia in the rate of the normal cycles. These influences are neurogenic and are carried by the extrinsic cardiac nerves. It may be inferred that their effect is manifested chiefly in the region of the sinus node, because in cases of auriculo-ventricular nodal rhythm respiratory arrhythmia is rarely if ever seen. While this inference is open to some question, it makes it possible, or even probable, that the point of origin of the stimulus giving rise to the abnormal waves is close to, or part of the sino-auricular node. This suggests the possibility of a condition of block within the sino-auricular

node with separate portions of the node originating different sets of P-waves.

We have found only one case similar to these in the literature. Schrumpf,<sup>1</sup> in 1920 reported the case of a man, thirty-seven years old, with rheumatic heart disease, mitral regurgitation, aortic insufficiency, and myocardial insufficiency, who, in a state of digitalis intoxication showed a tracing similar in many respects to the tracing from our Case 1. In his patient the apparent double auricular rhythm persisted for three days and disappeared as the digitalis intoxication subsided. He believed that because in many instances the P-waves and the abnormal waves were very close, they could not arise from the same nodal tissue, because of the refractory period of nodal tissue.

He pointed out the desirability of demonstrating a double set of auricular waves in the venous pulse tracing, corresponding to the two sets of apparent P-waves in the electrocardiogram. This could not be done in his case because dyspnea made it impossible to take venous pulse tracings. To support his opinion that the two auricles contracted separately he presented the synchronized electrocardiographic and venous pulse tracings from a patient with broad notched P-waves in which he found a double auricular wave in the venous pulse tracing corresponding to the two peaks of the P-wave. This tracing is suggestive but not entirely convincing. He concluded that the best explanation of the curve was that the Keith-Flack node was of dual character, that its two parts were associated with the two sides of the heart, that the two parts were completely dissociated, and that one auricle followed each part of the node.

In explaining the fact that the ventricles always followed the same set of auricular impulses he considered it probable that one set of impulses was relatively weak and that a condition comparable to auriculo-ventricular block existed between the portion of the node giving rise to the weak set of impulses and the auriculo-ventricular node, while the impulses giving rise to the other set of P-waves were stronger and the ventricles followed these as usual.

Schrumpf's article is a case report and is not supported by experimental work. It is of interest because of the similarity of the electrocardiograms from his case and with those from ours and because of his suggestion of the duality of the sino-auricular node.

Pace<sup>2</sup> described the gross and microscopic form of the sinus node in the heart of a sheep which he studied. In addition to the portion of the node extending from above downward and to the right in the region of the cavo-auricular sulcus, he found a prolongation extending from the upper end downward and to the left in the cavo-auricular cone, terminating in the interauricular septum. He did not generalize regarding these findings but thought it likely that they were an anomaly of the heart of the animal he studied.

Bruni,<sup>3</sup> at the same time as Pace, published a detailed anatomical study of the region of the sino-auricular node. He studied the region in embryos of the sheep and ox, and selected the 20 cm. ox embryo for a detailed description because at this stage of development the structures were particularly well shown, and the node could be reconstructed in detail accurately. He was able, however, to show the same general structure in hearts up to term.

In the 20 cm. fetus the node consisted of a body in the form of a quadrilateral plate in the region of the terminal sulcus on the external surface of the anterior part of the superior vena cava, coming in contact with the pericardium. This plate extended into the sinus portion of the right auricle. Several branches of nodal tissue were described extending from this plate, one from each anterior corner, left and right, the one on the left terminating in the interatrial sulcus. These were short and conical in form. Another, longer than these, extended up the right anterior wall of the superior vena cava. Two prolongations extending obliquely in a caudal and ventral direction are of particular interest. One extended in the wall of the right auricle from the right side of the central plate toward the inferior vena cava but did not reach it. The other extended from the left side of the central plate into and through the interauricular septum. No direct communication between either of these branches and the node of Tawara was demonstrated.

The studies of Pace and Bruni have this in common: they both found extensions of sinus nodal tissue into the interauricular septum.

Géraudel<sup>4</sup> makes reference to this work and to an anatomical study by Segré, who, in serial sections from four human hearts, two in fetuses, one in a newborn, and one in a young person, demonstrated a horseshoe shaped mass of nodal tissue in the superior vena cava. The left branch of this nodal tissue extended into the interauricular septum. This left branch he termed the node of Pace and Bruni. Géraudel was unable to demonstrate this left sided nodal tissue in adult hearts but thinks that the work of the several men on this subject deserves further consideration.

Roversi<sup>5</sup> reviewed the findings of Pace and Bruni in animals and reported experimental work of his own on dogs in support of their work. He believed that there were two masses of sino-auricular nodal tissue connected by specific conduction tissue. He also believed that the original node of Keith and Flack initiated the impulse, which was transmitted to the node of Pace and Bruni and thence to the ventricles. According to his conclusions the latter node could assume the functions of pace-maker in the event the node of Keith and Flack was destroyed. He was able to demonstrate to his own satisfaction, experimentally, that if the conducting tissue between the nodes was destroyed two P-waves resulted electrocardiographically. He interprets Schrumph's curve ac-

cording to his work to indicate a dissociation of the two parts of the sinus node. He agreed with Schrumpf's conclusion that it was probable that each auricle had its separate node and could be stimulated independently.

One weakness of his argument in explaining the double auricular rhythm is the lack of evidence for his contention that the two auricles, as units, can be stimulated to contraction separately. Inasmuch as it is generally believed that an auricular stimulus spreads by way of the ordinary myocardial tissue through both auricles, more evidence than he presents will be necessary to prove the hypothesis.

Borman and Meek,<sup>6</sup> in a study of hearts in dogs in which the sinus node had been destroyed by radon, found that the impulse arose in the region of the coronary sinus. This was in accord with the previous findings of Eyster and Meek. The latter, destroying the node surgically, found a shortened P-R interval when the sino-auricular node was not active. Borman and McMillan,<sup>7</sup> using radon, obtained normal electrocardiograms with the sinus node destroyed. These findings are interesting in connection with a possible double auricular rhythm, if we consider the possibility of a dissociation of the sinus node and the region of the coronary sinus, with both of them giving rise to stimuli at regular but different rates. An added difficulty arises in fitting this conception to our curves, however, in that the two centers are in the same auricle.

In spite of the fact that we do not consider the conception of the dual character of the sino-auricular node adequately proved, we are unable to controvert it, but can only raise questions and objections. It offers an explanation of the curves we have seen which would be difficult to make under other circumstances, although other possibilities must be considered. Two of the chief alternative hypotheses are: first, that the independent waves represent auricular extrasystoles which are not followed by ventricular responses, and second, that the electrocardiographic deflections are due to some extracardiac influence. The first is open to one of the same objections as Roversi's hypothesis, that is, the impulse giving rise to the auricular extrasystole is never propagated to the ventricles. The second seems unlikely, because in the two cases in which there is a sinus arrhythmia in the rhythm of the normal complexes the rate of the abnormal waves is variable to some extent and the variations occur in rather close harmony with the sinus arrhythmia of the normal complexes, though not to the same extent.

The papers of Schrumpf, Pace, Bruni, Roversi and Segré suggest the existence, perhaps as an anomaly, of a potentially double sino-auricular node, the two elements of which may be dissociated under rare conditions by what might be termed an intranodal block. We are unable to come to any conclusions about the mechanism producing these electrocardiographic manifestations. In any event the existence of such curves in the presence of disease processes known to produce defects in intra-

cardiac conduction probably should be regarded as evidence of myocardial change, even in the absence of any other objective sign of the latter.

#### SUMMARY AND CONCLUSIONS

Some curves are presented showing an unusual transient disturbance of rhythm, associated in all instances with other cardiac signs or symptoms. No adequate explanation for the formation of the curves is given, although possible mechanisms are discussed, among the most likely being intranodal block. When encountered in the course of pathological processes potentially damaging to the conduction mechanism of the heart such as those present in acute rheumatic fever, diphtheria, arteriosclerosis and others, they probably should be regarded as confirmatory, if not conclusive, evidence of such damage.

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## INCIDENCE AND DEVELOPMENT OF HYPERTENSION AND HEART DISEASE IN RAILROAD EMPLOYEES\*

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IN THE past four years 1,390 physical examinations have been made in the office of the Division Medical Examiner of the Chicago, Burlington, and Quincy Railroad. Of these, 618 were made on prospective new employees, 679 were service reexaminations, while 93 were examinations either for promotion or for increase in relief benefits—a term which really signifies increasing the insurance carried for them by the company, the premiums being deducted from their wages.

While becoming a member of the "relief" is not compulsory, nearly 100 per cent of the employees on our division are members. They must pass as good an examination to be employed as to become a relief member. Besides requiring a physical examination on all prospective new employees, the medical department of the road also has decreed that all old employees having anything to do with the running or maintenance of trains and equipment shall have a physical examination at least every two years. This includes engineers, firemen, conductors, brakemen, flagmen, yardmasters, switchmen, switch tenders, dispatchers, wire chiefs, telegraph operators, crossing gatemen, bridge and building foremen, derrick engineers, and section foremen. If at any time anything develops in the examination of one of these men which would make it expedient to see him more often than every two years, he is notified each year to appear for examination. These examinations are compulsory, *and a man may* be held off duty until examined if he is somewhat dilatory about going to the examiner's office. Usually, in order to help the men to remember, the examinations are arranged to take place in their birth month; and besides that they are notified by mail when their examination is due. Engineers are ordinarily examined every year after the age of fifty and every six months after the age of sixty. If they continue in good physical condition, they are retired and pensioned at seventy.

It is evident that we have had an unusual opportunity for examining a group of men at regular intervals. The development of symptoms and pathological findings has been noted with great interest. There is no question as to when one will again see the patient. We know he will report for examination at a certain time, and if we wish to see him more often, we merely request that he come in every three months or every month if necessary to check up his physical condition. The great majority of the men are interested in keeping fit, and they usually receive and act upon any suggestions for their physical betterment with an admirably cooperative spirit.

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\*Read before the Iowa Heart Association, Iowa City, Iowa, January 30, 1932.

The total number of examinations of prospective new employees and of those for promotion or increase in relief insurance was 711; of these 60, or 8.43 per cent, were rejected—practically one out of every twelve. Half of these rejections, or 30 cases, were due to hypertension, heart damage, or a combination of the two. The other 30 men were rejected for the following reasons: diabetes 9, defective vision 6, hernia 3, albuminuria 3, acute urethritis 3, color blindness 2, hypotension 1, defective hearing 1, convulsive syncope 1, and ankylosis of the elbow 1. However, we repeat that one-half of the rejections, or 4.22 per cent, was due to hypertension, heart damage, or both. This is practically one man out of every twenty-five.

The arbitrary upper limits for blood pressure for acceptance as a new employee are 150 mm. systolic and 100 diastolic. Evidence of organic heart disease is sufficient to reject the applicant.

It is interesting to note that only one case of hypertension in association with lues was seen, one case of hypertension and diabetes, and, strangely enough, one case of hypertension and pulmonary tuberculosis.

As mentioned before, 679 service reexaminations have been made. Of course, some men have had several examinations, so that there have not been 679 different individuals. However, we have a list of 74 employees who are now coming in for reexamination at intervals of one year or less. Practically all of these are on the frequent reexamination list because of hypertension, heart disease, or both.

In the past sixteen months there have been four deaths among employees who were being regularly reexamined. Of these only one was unexpected. This was a machinist sixty-six years old who had been in an automobile accident only six and one-half months previous to his death. He was not badly injured but was not passed for work for a period of two months because of some slight evidence of heart weakness. He had a slight hypertension and evidence of arteriosclerosis. He dropped dead in a bank. I have wondered whether accidents, in these older people, in which the injuries are apparently not serious, may not be much more important than we are inclined to think, especially in the upsetting of the circulatory balance. The other three deaths were all due to coronary thrombosis, two associated with marked and one with moderate hypertension. The two men with marked hypertension were forty-three and fifty-one years old, respectively. The man with moderate hypertension was sixty-three years of age. This sixty-three-year-old switch tender had advanced sclerosis. An interesting point was that in the regular reexamination made less than three months prior to his death he complained of pain in the right wrist and hand in the ulnar nerve distribution area. Two days before death he complained rather bitterly about the neuritis in his left elbow and shoulder. He lived only nine hours after the onset of his acute coronary symptoms. The fifty-one-year-old engineer died suddenly just after getting dressed in the early morning in preparation to drive out the fast mail.

The number of engineers who have died at the throttle is relatively very small. Dr. D. B. Moss, the chief medical officer of the Burlington Railroad, has told me that he knows of only one. The forty-three-year-old fireman died on duty about one hour after acute symptoms appeared. He was luetic, had been reexamined frequently, and the progressive aortic lesion had been watched with the expectation that sudden death might arrive at any time.

Of the 74 whom we are watching closely and examining at more or less frequent intervals, there are six with proved syphilis. These men are watched very closely, as we feel that Dr. Carey F. Coombs is right when he states that aortitis is the inevitable lot of the syphilitic who is inadequately treated in the early stages of the infection. Practically all of the luetic patients that I see at present have been inadequately treated. Incidentally I feel also that Stroud of Philadelphia is right in prophesying that we should be prepared for an increase in the incidence of syphilitic aortitis in the next ten to twenty years as an aftermath of the war. Aortitis seems to resemble tabes and paralysis in the period of the disease in which its appearance occurs; i. e., about twenty to twenty-five years after the primary infection.

Of the six luetic employees we are watching, five are engineers and one is a switchman. The switchman has some perforations of his palate and his uvula is missing, but so far his circulation has been good, with a blood pressure of 144/98 and no sign of heart or aortic damage. Only one of the engineers is in difficulty. He has beginning tabes and one of the most labile types of blood pressure I have ever seen. It has been recorded at varying levels from 114/90 up to 220/130. At present it has rather stabilized itself at about 190/120.

Blood pressure readings are considered important in this group, as any evidence of persistent drop in the diastolic pressure after other signs of aortic involvement have been found must mean aortic valve insufficiency. If the aortic valves become incompetent, then there must be considerable involvement of the mouths of the coronary arteries, with consequent narrowing, and sooner or later thereafter there is noted a lessening of the pulse pressure which indicates ventricular weakness—the next stage in the downward grade.

The remaining 68 are all seen because of heart damage, high blood pressure, or both, with the exception of one who is seen because of a fairly persistent hypotension of about 100 systolic. Of these 67 only three are seen because of the heart alone (all three being rheumatic hearts), 25 are seen only on account of hypertension, and the remaining 39 have evidence of heart damage and hypertension.

Most of the hypertension cases are of moderate grade, ranging from 160 systolic in the younger men, or 170 in the older men, up to 190. A very few—only three, I believe—are or have been above 190 systolic. One fireman was found to have a pressure of 210/124 at forty years of age. After some infected teeth were removed, the pressure dropped

to 180/114, and after tonsils were removed it was 164/114. The relatively slight decrease in the diastolic pressure is noteworthy.

It has been observed that, among the younger men, many whose blood pressure had been slightly increased showed a return to normal after the removal of abscessed teeth. It is felt that the suggestions which may be made at the time of the regular service reexaminations may be of importance to the employees.

We have been accustomed to change a man from the biannual to the annual examination if his blood pressure has increased 20 points or more since the last examination, or if the systolic blood pressure is 155 or above or if the diastolic blood pressure is 100 or above. He is also advised concerning the eradication of foci of infection, and we find that infected teeth in these employees are very common and also rather difficult to have removed. Our campaign against abscessed teeth is bearing some fruit, however, and we feel that the educational feature of the measure is sinking in.

The progressive features of circulatory degeneration in some of the cases have been particularly engrossing. The progressive steps in this degenerative process might be listed in a general way as follows: 1, gradual increase of hypertension; 2, appearance of an accentuated aortic second sound; 3, appearance of systolic aortic murmur sometimes closely followed by systolic murmur at apex; 4, gradual diminution of the diastolic blood pressure, with appearance of a to-and-fro aortic murmur or sometimes of ventricular weakness without appearance of aortic insufficiency; 5, in many cases circulatory accidents, either of the cerebral or coronary type.

Several men have been retired because of disabilities which have been considered to be too dangerous to the lives either of themselves or of those entrusted to them. Among these are an engineer, retired because of coronary thrombosis, although it was very difficult to keep him in bed even for ten days after his heart accident. He is up and around but has some dyspnea on moderate exertion. Another is a dispatcher who was retired after an acute attack of uremia with convulsions. It was felt that we should not further entrust the direction of the movement of trains to him. One switchman was retired of necessity after a hemiplegia. One engineer was retired because of slight hypertension and sclerosis with paresthesias of one arm and leg. One year later he suffered a hemiplegia and died in a very short time. A conductor was retired because of hypertension and evident heart damage with sclerotic aortitis.

It is to be hoped that all of our private patients may some day see the wisdom of regular physical examinations, for I believe that the early symptoms of many disturbances may be detected, and the process checked, if their physicians are only given a chance to see them at regular intervals.

# A CASE OF TUBERCULOUS PERICARDITIS WITH EFFUSION TREATED BY MEANS OF PNEUMOPERICARDIUM\*

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THE injection of air into the pericardium as a therapeutic procedure in pericarditis with effusion was first reported by Wenkebach in 1910.<sup>1</sup> In his patient, who had pulmonary tuberculosis as well as a large pericardial effusion, repeated taps without the injection of air failed to prevent the rapid reaccumulation of the fluid, but following the injection of air in amount equal to about half that of the fluid removed, the reaccumulation was much slower and the general condition of the patient improved. Wenkebach followed his case for a year and a half and in that time did nine taps followed by air injections. At the end of this time the patient was greatly improved.

Following this successful case, which was also reported by Gesellschaft in 1910,<sup>2</sup> Alexander in 1911,<sup>3</sup> Hansen,<sup>4</sup> and Émile-Weil and Loiseleur,<sup>5, 6</sup> in 1916, Meyer<sup>7</sup> in 1918, Martinet<sup>8</sup> in 1921, Castex<sup>9, 10</sup> and Troisier, Jacquelin and Gayet<sup>11</sup> in 1923, Oppenheimer<sup>12</sup> in 1924, Rigler,<sup>13</sup> Rawls,<sup>14</sup> and Lian and Corneau<sup>15</sup> in 1925, Yacoël and Giroux,<sup>16</sup> and Castex, Carelli and Gonzalez<sup>17</sup> in 1926 each reported one case of probable or proved tuberculous pericarditis with effusion treated by tapping followed by injection of air, oxygen or nitrogen. Zuccola<sup>18</sup> reported three cases in 1925, one of rheumatic and two of tuberculous origin.

Without exception all the authors felt that the procedure gave symptomatic relief and slowed up the reaccumulation of the fluid. Of the sixteen patients with tuberculous pericarditis treated by pneumopericardium nine died while under observation, but of these in one only<sup>14</sup> did death seem related to the procedure. This patient died eight hours after the first air injection. Most of the others died of tuberculosis elsewhere in the body, usually pulmonary, after the pericardial symptoms had been largely or partially relieved. The seven patients who did not die under observation were not followed long enough to permit the drawing of definite conclusions, but several of them recovered sufficiently to resume partial activity.

The chief therapeutic advantage of the procedure has been thought to be the prevention of the rapid reaccumulation of fluid following tapping. In addition, it lessens the resistance the heart has to work against by substituting an easily compressed gas for a noncompressible liquid. Several authors have felt that it is possible to prevent the formation of adhesions by keeping the pericardium distended with air. A systematic effort to do so was made by Zuccola.<sup>18</sup> In two cases of tuberculous peri-

\*From the Medical Services of the Massachusetts General Hospital.

carditis he injected air several times after the fluid had disappeared, raising the pericardial pressure in the last taps from 5 to 12 and from 10 to 16 cm. of water, respectively. When these patients came to autopsy, several months after the last tap in each case, there were a few pericardial adhesions, especially about the apex of the heart. Zuccola emphasized the importance of injecting enough gas to keep the surfaces apart. It seems unlikely that the formation of adhesions could be prevented completely, for to do so the amount of air injected would have to be so great, in order to overcome the contraction of the scar tissue, that the pressure it would exert on the heart would be more than the latter could tolerate without failure. Possibly if a systematic attempt had been made to keep the pressure up in the case here reported, the adhesions would have been much less dense and the operation correspondingly easier and more successful.

#### CASE REPORT

A Portuguese boy of eighteen years came to the emergency ward of the Massachusetts General Hospital on August 26, 1930, complaining of attacks of vomiting for eight months and extreme shortness of breath for a few days. Family and past histories were irrelevant. There was no family history of tuberculosis.

The patient had always been very healthy and vigorous until shortly after a boxing bout eight months previously, when he developed mild epigastric and right upper quadrant, gnawing pain and tenderness associated with vomiting, which occurred a few minutes after meals. About the same time he developed a dull pain in the lower right chest which was most noticeable on leaning forward. He became rather short of breath and after two weeks or so of these symptoms he went to St. Luke's Hospital in New Bedford on December 28, 1929. A letter from this hospital states, "Physical examination of the heart at time of his admission showed the following: Right border 10 cm. to right of sternum by percussion, left border in axillary line. All this area is dull to percussion. Heart sounds are weak and quick. Rate 96. X-ray revealed (December 28, 1929) no evidence of fluid in chest. Heart shadow appears to be large, could be pericardial effusion. On January 1, 1930, heart shadow apparently smaller. Increased density in right chest from fourth rib in front to base. Diagnosis, pericarditis, acute, serofibrinous." No tap was done, nor was any specific treatment given other than general medical care. He improved and was discharged from St. Luke's Hospital on January 15, 1930.

Following discharge he continued to improve, had no more pain or vomiting and very gradually regained strength. The next two or three months he spent most of the time in bed, but as the spring advanced he gradually improved so that by June he was up all the time and did a little easy work such as raking lawns. He was, however, very short of breath, and whereas before his illness he had been able to swim several hundred yards without difficulty, he was now unable to swim more than ten strokes.

Two and one-half weeks before entry to this hospital the epigastric and right upper quadrant pain returned, accompanied by vomiting as before. A few days later there was swelling of the abdomen and some palpitation of the heart when lying down. For about two months he had had a cough with a small amount of sputum. He thought he had gained about twenty pounds during the illness.

The history was somewhat unreliable due to the limited intelligence of the patient. Physical examination at entry showed a well-developed and nourished negro.

sitting up in bed, taking rapid, shallow breaths. The veins in the neck were somewhat distended. Cardiac dullness extended to the axilla on the left and nearly to the axilla on the right. The apex impulse was not felt. The supracardiac dullness was 6.5 cm. The heart sounds were faint but perceptible at the apex and fairly distinct at the base. There were no murmurs or rub. The pulse was 80 and definitely paradoxical. The blood pressure was 120/95 mm. The lungs were clear although the diaphragm was high on both sides. There was no Ewart's sign. The abdomen was tense and somewhat distended; there was a fluid wave and shifting dullness. The upper border of the liver was obscured by the cardiac dullness, but the edge was felt 4 cm. below the costal margin on the right and extended across the epigastrium. There was no edema of the genitals or extremities.

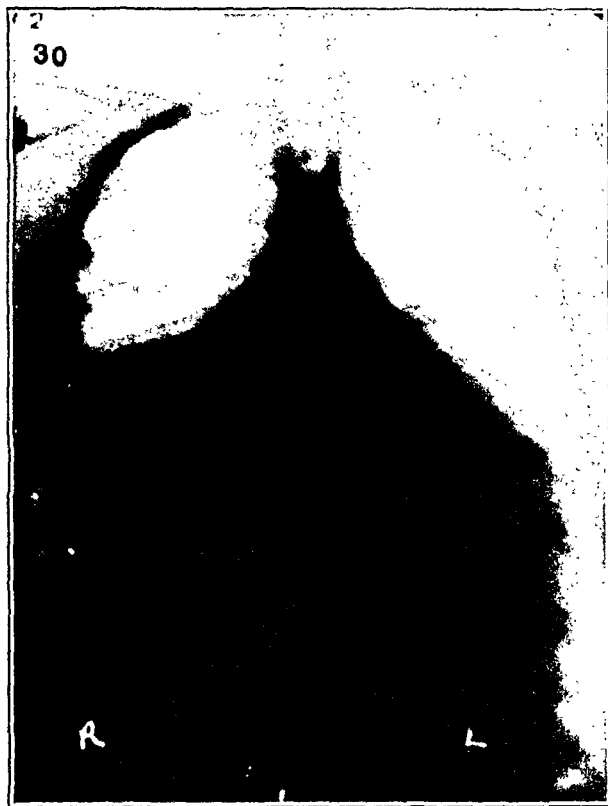


Fig. 1.—August 26, 1930. Shows the enormous size of the pericardial shadow on entry.

Laboratory findings on admission were a red blood cell count of 4,300,000, hemoglobin 85 per cent (Tablquist), white blood cell count 9,550, and blood smear not remarkable. The urine was negative.

The day after entry x-ray picture of the chest showed an enormous heart shadow extending almost to the axillary line on both sides. The cardiac pulsation could not be made out by the fluoroscope. The right costophrenic angle was obliterated. The appearance suggested a pericardial effusion with a small amount of fluid in the right pleural cavity. A chest plate taken when the patient was on his back showed only a slight increase in the width of the supracardiac shadow.

The consulting cardiologist, Dr. Paul D. White, thought that pericardial effusion, probably due to tuberculosis, was the most likely diagnosis and advised tapping.

On August 28, 1930, taps were done in the fifth left interspace and the fourth right interspace; both yielded what was thought to be blood, but the fluid was not examined at the time, and this neglect caused us to abandon the diagnosis of

pericardial effusion. The same day he became much worse; he was very orthopneic, had more cough with some frothy white sputum (repeated examination of the sputum was always negative for tubercle bacilli); he was put on the danger list. He required considerable morphine to control the dyspnea. The abdominal discomfort and vomiting became much worse. Venesection of 200 c.c. on August 29 gave slight relief. Digitalization was started and was complete by September 1, with resulting decrease in the orthopnea.

For the next two and one-half weeks he ran an up-and-down course, fairly comfortable at times and at others extremely orthopneic with much pain, nausea and vomiting. Abdominal paracentesis on September 9 yielded only 5 c.c. of yellow fluid which clotted before it could be examined. Culture of this was negative,



Fig. 2.—October 5, 1930. This plate was taken with the patient lying on his right side immediately after the first air injection. The air rose to the highest part of the pericardial cavity and moved freely from one part to another as was shown by plates in different positions.

and a guinea pig injected with it showed no tuberculosis at autopsy six weeks later. He received salyrgan intravenously every three to four days which caused moderate diuresis. Prior to this treatment he had gained 6 pound since admission (154 to 160); after it he lost 14 pounds.

On September 17, 1930, another pericardial tap was done and 120 c.c. of bloody fluid removed which had red and white blood cell counts about one-third that of blood taken at approximately the same time. The following day 450 c.c. more were removed. After this he had no orthopnea and was subjectively much improved. On September 20 and 26, 270 and 600 c.c. of fluid respectively were removed from the pericardium causing little noticeable clinical change in spite of marked subjective relief. For a time after this he refused to stay in bed, but soon pain in the lower right axilla developed (without physical signs), and he returned to bed of his own accord.

After considerable discussion it was decided that air be injected into the pericardium the next time fluid was withdrawn. On October 5, 375 c.c. of fluid were removed by the sub-xyphoid route and 200 c.c. of oxygen injected. He stood the procedure well. As each 50 c.c. of fluid was withdrawn the blood pressure rose



about 5 to 10 points, and when a similar amount of oxygen was injected, it fell about the same amount. The pressure of the fluid in the pericardium was measured by a manometer connected to the injecting needle; this varied from 8 to 20 cm. of pericardial fluid, the high points occurring when the patient strained. Pulse and respiratory oscillations were visible, the respiratory oscillations being only 1 to 2 cm. and the pulse barely visible. (The manometer was connected with the needle by approximately two feet of tubing which probably had a definitely dampening effect on the oscillations.)

X-ray pictures taken after the tap showed gas in the pericardium, and plates taken with the patient in different positions showed that the cavity was apparently continuous and the pericardium not especially thick. No succussion splash or "bruit



Fig. 3.—October 10, 1930. Taken after the third injection of air, shows the pericardium distended with air, and the heart not definitely enlarged. There is fluid in the right pleural cavity.

de moulin'' was audible after this tap, although resonance could be demonstrated by percussion.

Digitalis was omitted at this time because the patient refused to take it.

Since this first injection of gas resulted in no apparent ill effect, 740 c.c. more of fluid were removed and replaced by 590 c.c. of air on October 8, and 740 c.c. of fluid by 560 c.c. of air on October 10. During these taps venous pressure readings were taken which showed a definite fall when fluid was removed and a rise when air was injected. The venous pressure was always from 2 to 4 cm. of water greater than the pericardial pressure. Following the October 8th injection a succussion splash was heard, and the cardiac dullness was replaced by tympany. On October 11 he had marked respiratory distress, cough and abdominal pain which was not relieved by morphine, so 175 c.c. of air were removed. This came out under some pressure (not measured) and was followed by definite subjective relief. Several days later he developed pitting edema of the ankles which lasted for a short time, but he seemed to be much more comfortable and improved steadily. The liver edge,

which at first had moved lower until it reached the iliac crest, now began to recede and became much less tender. X-ray pictures taken two weeks after the last tap showed that approximately two-thirds of the air was still present. On October 29 a liver function test (tetra-bromsulphonaphthalein) showed no retention of the dye, while on August 26 and September 15 there had been 15 per cent retention. On November 2 he developed a pericardial friction rub.

He continued to improve, but as the x-ray picture showed that considerable fluid was still present, another tap was done on November 12. Only 25 c.c. of fluid were obtained, and, although there was undoubtedly more fluid there, further attempts to withdraw it were not made because the patient became very uncomfortable and upset. Following this tap he had a chill and fever amounting to 103.5° F., but the next day he again felt better.

An x-ray picture of the chest on November 22 showed that the air had been entirely absorbed but that fluid was still present or had reaccumulated, so he was tapped again the next day, this time in the fifth intercostal space on the right, and 320 c.c. of fluid removed and 250 c.c. of air injected. This tap also was followed by a chill and fever.

From November 21 to December 6 he was given 0.2 gm. of sodium cacodylate three times daily in the hope that it might hasten the absorption of the fluid.

Following this last tap he continued to improve until he was discharged on February 7, 1931. Taps were attempted on December 20 and 24, 1930, both failing to yield fluid. His temperature, which had been swinging from 99° to 101° F. by mouth the first three months he was in the hospital, was rarely over 100° F. by rectum in December. From the last of December until discharge the temperature was taken by mouth and showed, until the middle of January, an afternoon rise to 99°, after which it was usually 98.6° or less.

During the patient's stay in the hospital nine sputum tests were negative for tubercle bacilli, the von Pirquet test was negative, and dilute intradermal tuberculin tests were negative. Three guinea pigs injected with pericardial fluid, one with abdominal fluid, and one with sputum, were negative for tuberculosis at autopsy.

The week before discharge a final x-ray picture showed that the heart was slightly enlarged and that there perhaps was a small amount of air along the left border of the heart; fluid was not demonstrable, although there was a rounded area of dullness along the right border of the heart. The pericardium appeared about one-quarter of an inch thick; it was quite thin in pictures taken earlier in the course of the disease.

The patient was readmitted to the hospital on March 23, 1931, six weeks after discharge. In the interval he had grown stronger, gained three pounds, and was a little less short of breath. He had had almost continuous, right upper quadrant pain and soreness with three attacks of rather acute right upper quadrant pain radiating to the left shoulder and left side of the neck.

Physical examination showed very little change from his condition at time of discharge, although he appeared definitely stronger. The heart sounds were rather muffled but of fair quality. Blood pressure was 110/75 mm. The veins of the neck were distended. The pulse was paradoxical. The lungs showed a small amount of fluid at the right base. The abdomen was somewhat distended; dullness in the flanks and a fluid wave were present. The liver edge was palpable 6 to 8 cm. below the costal margin and was rather tender. There was no edema of the genitals or extremities.

X-ray pictures showed that the cardiac shadow had decreased somewhat in size. Stereoscopic films showed that the rounded area of dullness at the right side of the heart, about 3 cm. in diameter, was a small interlobar collection of fluid, not connected with the pericardium.

During a two weeks' period of observation his temperature was normal, pulse about 80, urine negative except for an occasional, very slight trace of albumin, and white blood cell count slightly elevated, 10,000 to 12,000. In view of the persistent engorgement of the liver and ascites it seemed probable that he had an adherent pericardium which was interfering with the action of the heart, and since there seemed to be nothing to gain by further rest and general care, cardiolysis was decided upon. This was done on April 16, 1931, by Dr. Wyman Whittemore. Sections of the third to seventh costal cartilages on the left were removed. The pericardium, one-third to one-quarter of an inch thick, was adherent to the heart, although a definite line of cleavage was present. The pericardium was gently peeled off the heart and large flaps cut away, first on the left side, then on the right. Posteriorly, particularly near the apex, the pericardium was more adherent and could not be removed. When the anterior portion of the thickened pericardium was



Fig. 4.—April 3, 1931. Taken two weeks before cardiolysis. The dullness at the right border of the heart was shown stereoscopically to be probably a small interlobar collection of fluid.

removed, the heart bulged into the opening thus formed; it seemed evident that its activity was much less hampered.

Pathological examination of the pieces of pericardium removed showed in one area a focal collection of epithelioid cells and lymphocytes, the appearance of which was sufficiently typical to justify a diagnosis of tuberculosis in the healing stage.

After the operation, which caused relatively slight shock, first serum drained from the incision, later pus from two sinuses in the scar. The patient ran an afternoon temperature of  $100^{\circ}$  to  $101^{\circ}$  by rectum until the middle of June. His pulse, still paradoxical, at first was 100 to 120, and later fell to 90 to 100. The white blood cell count varied from 11,000 to 15,000. The blood pressure remained low, 85-90/70. Digitalization had no definite effect on either the pulse or the urinary output, although with salyrgan a fair diuresis was obtained several times without causing any perceptible difference in the amount of fluid in the abdomen and chest.

His general condition and strength, however, gradually improved so that on June 26 he was discharged to Lakeville Sanatorium for general care. At the time of his discharge his condition was not so good as before operation; apparently the quiescent tuberculous process had become active again. It seemed likely that adhesions in the region of the right auricle and inferior vena cava were responsible for the continued ascites and other signs of venous obstruction, but further operative procedures in the presence of probably active tuberculosis seemed contraindicated.

A report from the Lakeville Sanatorium on October 30, 1931, states that the patient's general condition is good. At time of admission to that institution he was dyspneic and had considerable precordial pain. He was kept in bed and given one and one-half grains of digitalis daily with resulting disappearance of the dyspnea and precordial pain. He still had right upper quadrant pain.

Physical examination at the time of this report revealed regular heart sounds of good quality, rate 70 to 80. The liver edge was still palpable four to five finger-breadths below the costal margin, but there was no abdominal tenderness. There was still slight drainage from the sinus in the operative scar. His temperature had remained normal and the white blood count had been 8,000.

X-ray picture of the chest showed no essential change from that taken just prior to operation.

He had gradually increased his activities and was up and about for short periods daily.

#### SUMMARY

A brief review of the literature on therapeutic pneumopericardium is presented. A case of tuberculous pericarditis with effusion treated first by pneumopericardium then by cardiolysis is reported. From the present case and the few cases now in the literature it is impossible accurately to estimate the therapeutic value of artificial pneumopericardium. It did not cure this patient nor even prevent the necessity for operation later. This may have been because the treatment was not continued for a sufficiently long period. If one wishes to prevent the formation of pericardial adhesions in pericarditis, it would seem, on theoretical grounds, preferable to keep the parietal and visceral pericardium apart by means of elastic gas rather than by inelastic fluid. The method of artificial pneumopericardium therefore would seem to deserve more extensive trial than it has yet been accorded.

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## ANEURYSM OF THE AORTA PRODUCING PULMONARY STENOSIS AND BUNDLE-BRANCH BLOCK\*

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IT IS uncommon for an aneurysm of the aorta to encroach upon the pulmonary artery, conus arteriosus, or right auricle, or to invade the interventricular septum. In some instances such aneurysms are of congenital origin being due to defective development of the bulbar septum and are, in consequence, often accompanied by interventricular septal defects. These aneurysms are usually small. They arise from a sinus of Valsalva and project into the conus of the right ventricle where, as a rule, they finally rupture. Abbott,<sup>1</sup> in reporting a case of this nature, reviewed the literature and discussed the developmental defects which cause the condition.

Acquired aneurysms of this group are relatively more frequent and usually follow luetic aortic disease. Their common site of origin is higher than that of the congenital type and they more commonly project into the pulmonary artery than into the right ventricle. Scott,<sup>2</sup> in 1924, described two cases in which rupture into the pulmonary artery had occurred and reviewed the literature of the acquired type up to that date. Since then a few additional cases have been reported. Gunn<sup>3</sup> described an aortic aneurysm which appeared to have produced compression of the pulmonary artery into which it finally ruptured. Rothschild, Sacks, and Libman,<sup>4</sup> in a discussion of the disturbances of cardiac mechanism in subacute bacterial endocarditis and rheumatic fever, mention briefly one case in which a mycotic aneurysm of a sinus of Valsalva projected into the interventricular septum and caused partial bundle-branch block. They state that serial sections demonstrated that the aneurysm had partially intercepted the path of the left branch of the bundle of His. Buffalini<sup>5</sup> reported a case in which two aneurysms arose from the first part of the aorta and encircled the pulmonary artery, thus causing stenosis. This case was presented in greater detail by Costa<sup>6</sup> who also described another in which an aneurysm had perforated into the pulmonary artery. Laederich and Poumeau-Delille<sup>7</sup> reported an aneurysm which projected into the right auricle where it finally ruptured. The case of Stejfa<sup>8</sup> in which an aneurysm the size of a walnut caused compression of the pulmonary artery and also, he believed, block of the "left branch of Tawara's node" will be discussed in greater detail later. Schwab and Sanders<sup>9</sup> reported a case of acquired aneurysm which had ruptured into the right ventricle and they were able

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to find only two previous cases of this nature in which such an occurrence had taken place. The following case is presented because of the unusual growth direction taken by the aneurysm and because of interesting pathological changes which it appeared to have caused.

#### CASE REPORT

*History.*—R. L., an intelligent colored man, aged thirty-six years, a motor mechanic by occupation, came to the Cardiac Clinic of the Long Island College Hospital on June 5, 1929. He complained of dyspnea, palpitation, weakness, abdominal swelling and constipation. Five years previously, he commenced to suffer from dyspnea on exertion, marked palpitation and weakness, and he received medical treatment which relieved him to some degree. During the last six months all of these symptoms had become progressively worse and the patient noticed that his abdomen had been considerably distended. Dizziness had been gradually increasing during the past five months and he had fainted on one occasion. On admission to the Clinic he could walk only a short distance without marked discomfort. Both dyspnea and palpitation were extremely marked on any exertion but precordial pain was absent.

*Previous Illnesses.*—At the age of sixteen the patient suffered from gonorrhea and syphilis with secondary manifestations. He received a series of mercurial injections in a hospital in Philadelphia but on leaving the hospital he discontinued treatment.

*Family History.*—Nothing of note except that his wife had never been pregnant.

*Physical Examination.*—The patient was a well built colored man weighing 195 pounds. Even slight exertion caused considerable dyspnea. Slight cyanosis of the lips was present but there was no edema. The pupils were equal and reacted to light. Marked pulsation of the vessels of the neck was seen, the arterial pulsation being much more marked than the venous. The radial pulse rate was 72 beats per minute with some irregularity due to extrasystoles. Both pulses were equal and there was evidence of sclerosis of the peripheral vessels. The blood pressure was 130/65 mm. A suggestion of a capillary pulse was present but no peripheral signs of aneurysm were elicited.

*Heart.*—There was a heaving diffuse pulsation all over the precordium and the apex beat was felt in the 6th interspace 15 cm. from the midsternal line. No thrill was present over any area. The heart was markedly enlarged both to the left and to the right and on the left side there was a slight prominence in the region of the pulmonary conus and left auricle. The aortic arch did not appear widened. On auscultation there was noted a very loud, rasping systolic murmur, which was maximal in the second left interspace but could be heard over the whole precordium and also in the vessels in the neck. A diastolic murmur, of which the point of greatest intensity was in the second and third interspaces, was heard to the left of the sternum and was transmitted faintly over the rest of the precordial area. The second sound was almost inaudible over the entire precordium. An occasional râle was heard at the bases of the lungs. The liver was slightly enlarged. The nervous system showed no abnormality.

*Electrocardiogram.*—The auriculo-ventricular conduction time was slightly prolonged (0.22-0.24 sec.). A marked degree of partial right bundle-branch block (new terminology) was shown as the QRS complex was 0.15 sec., the main initial deflection was negative in Lead I and positive in Lead III with T opposite to the main deflection in each lead (Fig. 1). An irregularity, due to extrasystoles which appeared to arise in the upper septal region of the ventricle, was also found.

*X-Ray and Fluoroscopy.*—The heart was tremendously enlarged both to the right and to the left. (Cardiac Index 0.8.) The right side was of a globular shape and the left side was unusually straight with a slight prominence in the region of the pulmonary conus and left auricular appendix. The aortic arch was not widened and no evidence of aneurysm was seen. (Fig. 2.) On fluoroscopy no aneurysm was ap-

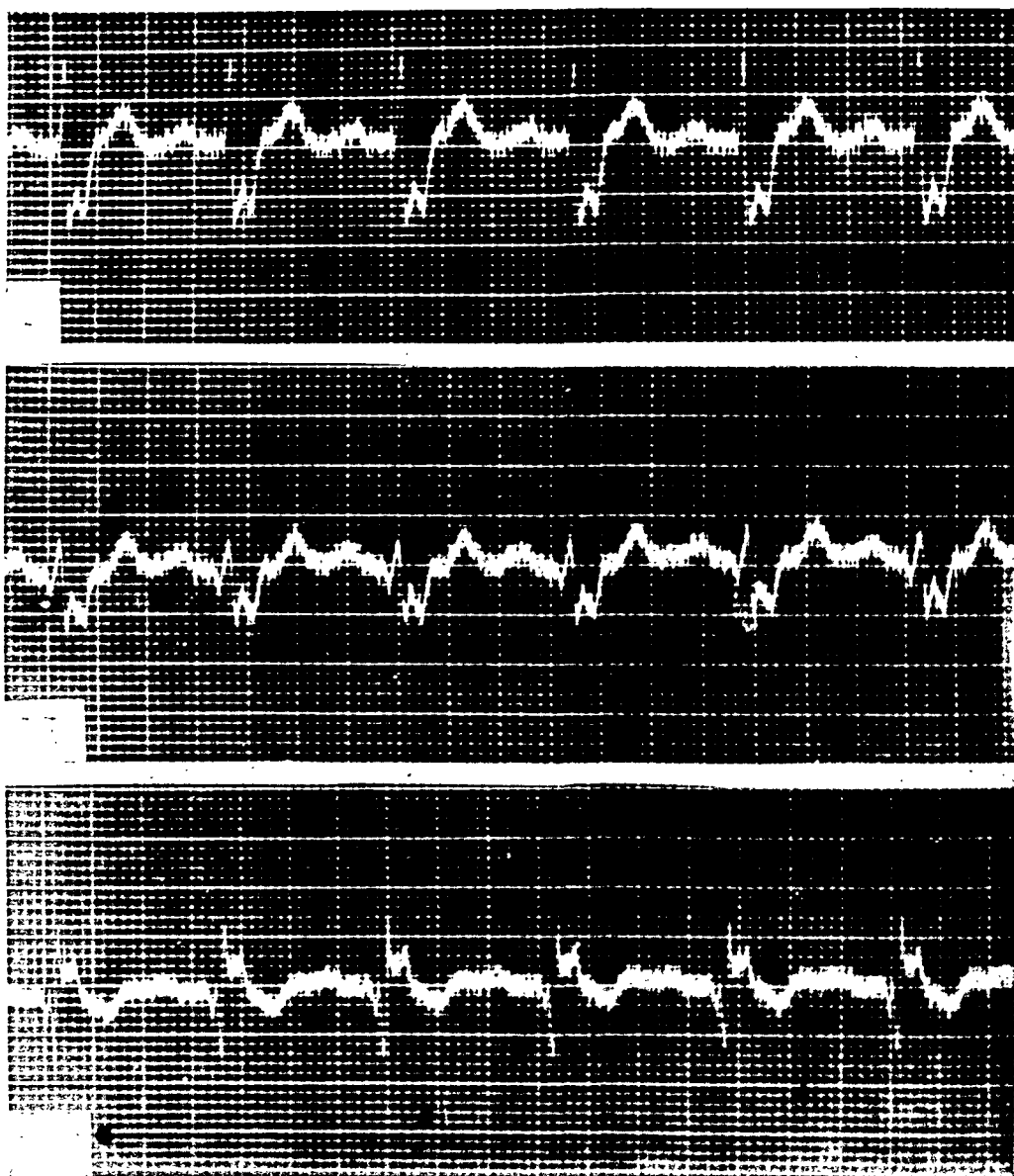


Fig. 1.—Electrocardiogram taken on July 2, 1929, indicating a high grade of bundle-branch block.

parent and the posterior mediastinal space did not appear to be encroached upon more than is usual with hearts of this size.

*Laboratory Examinations.*—The Wassermann test, although frequently repeated, was positive on only one occasion when it was +2. Other laboratory findings were normal.

The opinion was expressed that the patient was suffering from tertiary syphilis and aortic insufficiency with gummatous lesions producing the bundle-branch block.



As this did not appear to cover all of the findings, it was considered possible that congenital pulmonary stenosis was also present.

*Treatment.*—Complete rest in bed at home was ordered and mercury and potassium iodide were given by mouth.

*Progress Notes.*—As the patient did not show any improvement, he was admitted to the Long Island College Hospital on June 13, 1929. At this time the only change in the condition was that pulsus bigeminus was present. The site of origin of the extrasystoles as shown by the electrocardiogram had changed from the septal region to the wall of the right ventricle. The same treatment was continued and, in addition,

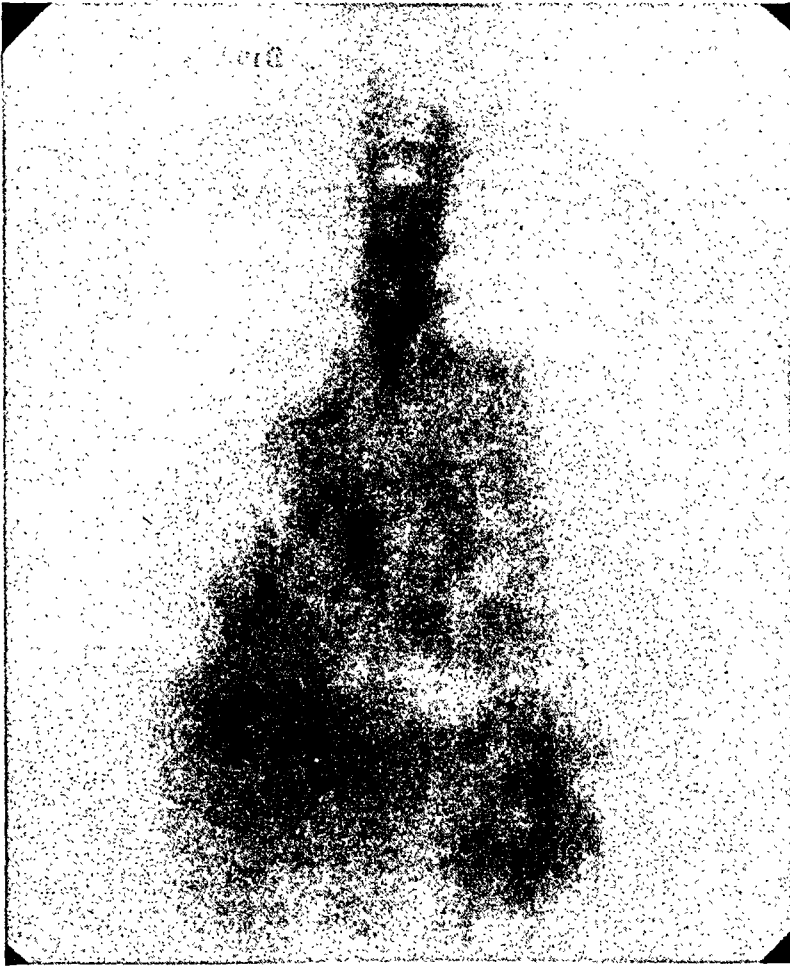


Fig. 2.—X-ray of heart (6 foot plate) taken on June 3, 1929, showing marked enlargement of both left and right ventricles.

the patient was fully digitalized. The extrasystoles soon disappeared and the patient slowly improved. The patient was discharged from the hospital on July 20, at which time he was able to take mild exercise without marked discomfort. He visited the Clinic at intervals during the next nine months but his condition became gradually worse until he finally became bedridden. On March 22, 1930 he was readmitted to the hospital. No marked dyspnea was noted while at rest and the heart showed no significant change since the previous admission. Fluid was present in the right pleural cavity and the liver was enlarged 12 cm. below the costal margin but there was no edema of the extremities. The x-ray and electrocardiographic findings at this time were the same as before. As the patient had been on a maintenance dose of digitalis, this was continued and potassium iodide was given in large

doses. At first there was some improvement in the condition and the fluid in the pleural cavity disappeared. Soon, however, he began to grow worse. The liver became progressively larger while edema of the extremities and ascites appeared and increased despite the administration of various diuretics. He died on May 6, 1930.

*Autopsy No. 1340. May 6, 1930.*—Marked edema of the extremities and of the tissues of the abdominal and thoracic walls was found at autopsy. A frothy, blood-tinged fluid exuded from the mouth and nose. There were otherwise no external abnormalities of note.

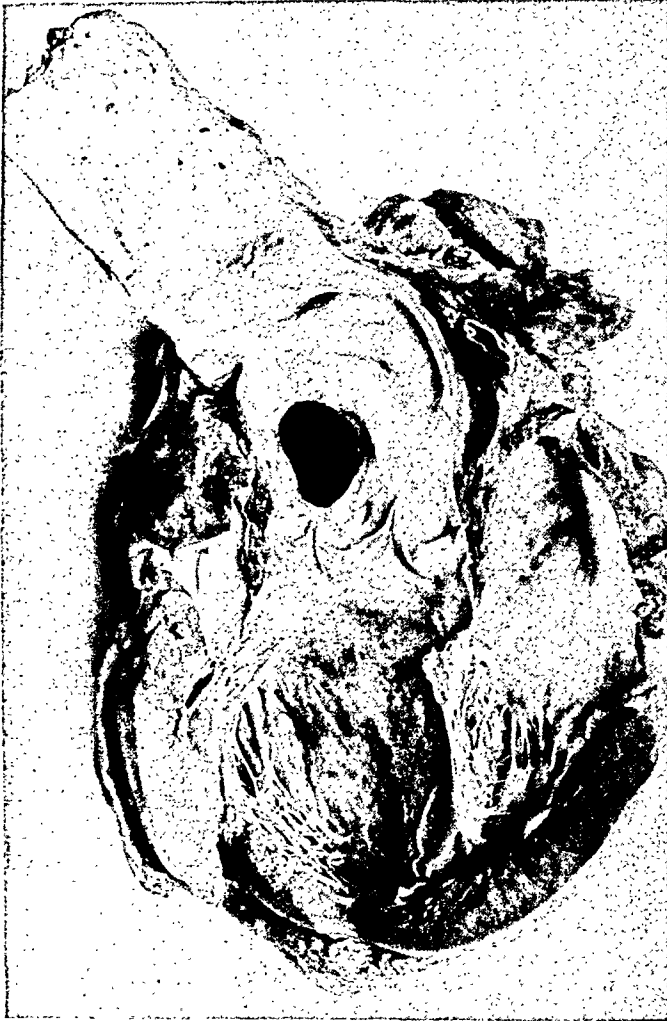


Fig. 3.—View of the left ventricle and aorta showing the orifice of the aneurysm. The luetic puckering of the aorta and the blotchy discoloration of the septum can be seen.

The pericardial sac was greatly enlarged, partly through the presence of about half a liter of clear, straw-colored transudate and partly because of great enlargement of the heart. The distended sac measured 20 cm. in its greatest transverse diameter. Both the parietal and visceral layers of the pericardium were markedly thickened and numerous recent adhesions were found at various points.

The heart was enormously enlarged, its weight being 975 grams. This enlargement was due to hypertrophy and dilatation of both ventricles and to a particularly marked dilatation of the right auricle. A firm rounded mass presenting on the anterior aspect of the heart between the right auricle and the conus arteriosus also contributed to the general enlargement.

On opening the chambers of the heart and the great vessels a saccular aneurysm of the ascending aorta was found. It was roughly spherical in shape, measuring 9 cm. in average diameter and was about half filled with lamellated thrombus. The orifice of the aneurysm was circular, 3 cm. in diameter, and the edges were rounded and smooth. Its lowest point was 1 cm. above the commissures of the right and left cusps of the aortic valve (Fig. 3). In its growth the aneurysm had pushed forward compressing the base of the pulmonary artery and the conus arteriosus. It had also pushed downward into the tissue of the interventricular septum and outward into the base of the right auricle. Superiorly it presented as a firm rounded mass between the pulmonary artery and the right auricular appendix.

The aorta measured 8 cm. in circumference at its base, which was the widest part. The ascending portion showed the typical scarring and intimal hyperplasia of luetic mesoarteritis. The sinuses of Valsalva and the coronary orifices were not particularly involved in the luetic process. The aortic valve cusps were noticeably shortened in their vertical dimensions, moderately thickened, and the edges somewhat rolled. The

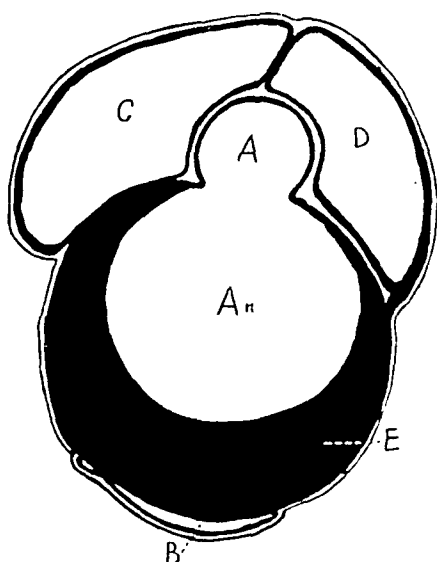


Fig. 4.—Diagrammatic representation of a cross section (roughly to scale) immediately above the aortic valve, showing compression of the pulmonary artery by the aneurysm. *A*, aorta; *An*, aneurysm; *B*, pulmonary artery; *C*, right auricle; *D*, left auricle; *E*, lamellated thrombus in the aneurysmal sac.

right and left cusps showed a 2 mm. separation at their commissures. The valve was incompetent to some extent.

The base of the pulmonary artery and the conus arteriosus had been so compressed by the aneurysm that a transverse section in the region of the pulmonary valve showed a crescent-shaped lumen with the opposing walls partially in contact with each other. At one point, immediately above the valve, there were organized adhesions between the opposing surfaces (Fig. 4). The right and left cusps of the pulmonary valve were tightly stretched over the bulging aneurysmal mass and appeared incapable of functioning. The portion of the aneurysm which presented in the conus consisted of a very hard rounded shell of connective tissue over which a glistening layer of endocardium was stretched. No remains of heart muscle were grossly visible in this area. Immediately below the left cusp of the valve the aneurysm showed a small, softened, necrotic patch, of a dirty gray-brown color contrasting sharply with the pale surrounding connective tissue. Perforation into the conus at this point seemed imminent (Fig. 5).

Both right and left ventricles were enormously hypertrophied and dilated. The right auricle was also markedly dilated while the left auricle was approximately normal in size. The tricuspid valve ring measured 13.5 cm. in circumference.

As noted above, the aneurysm had pressed down into the base of the inter-ventricular septum near its anterior limit and in this situation a zone of "pressure atrophy" with fibrosis adjoined the wall of the aneurysm. Irregular grayish patches of fibrosis, reddish streaks of granulation tissue, and yellow-brown areas of recent necrosis were scattered throughout the remainder of the septum.

The coronary vessels were explored as far down as could be reached with fine scissors and probes but no thrombosed vessels were found. The anterior descending branch of the left coronary artery was markedly constricted as it curved around the



Fig. 5.—View of the right heart showing A, the aneurysm bulging into the conus; B, the distorted pulmonary valve cusps; C, the area of necrosis in the aneurysm; D, the fusion of opposing surfaces of the pulmonary artery.

aneurysm, while beyond this area it was of normal calibre. The first portion of the right coronary was similarly constricted.

The pathological changes in the rest of the body may be summarized as those of chronic passive congestion and anasarca. Death appeared to have been due to myocardial failure.

An attempt was made, through a study of serial sections of the septum, to identify the bundle of His and its main branches in order to determine the location of the block which had been electrocardiographically established. Sections were cut transversely through the entire upper portion of the septum. The wall of the aneurysm consisted of dense hyalinized connective tissue containing deposits of calcium salts. Merging with the aneurysmal wall was a zone of fibrosis in which but few remains

of heart muscle were found, while the remainder of the septum showed a considerable amount of scar tissue, granulation tissue, and heart muscle in various stages of degeneration and necrosis. Occasional small granulomatous lesions, interpreted as being miliary gummata, and extensive small round-cell infiltration were also found. Because of the extensive necrosis and fibrosis the conduction pathways could not be identified with certainty.

The microscopic sections of the ascending aorta showed typical mesaortitis luetica while slight scarring, marked edema, cloudy swelling, and hydropic degeneration were seen in those from the ventricular walls.

#### DISCUSSION

In the reported cases of aortic aneurysm projecting into the pulmonary artery or right ventricle, both congenital and acquired, the diagnosis rarely has been made before rupture. Indeed, except in the congenital cases with an associated septal defect, it was unusual for symptoms to be present before perforation had taken place. After this event there appeared pathognomonic symptoms, which have been described fully both by Abbott<sup>1</sup> and by Scott.<sup>2</sup> Only two cases have been found which closely resembled that described above, one by Rothschild and his coworkers<sup>4</sup> and another by Stejfa.<sup>8</sup> The former was only incidentally reported with few details while the latter was fully discussed. Stejfa made a diagnosis of aortic aneurysm compressing the pulmonary artery on the basis of a rough systolic murmur heard in the second and third left interspaces with enlargement of the heart to right and left. In addition, there were signs of aortic insufficiency while a tracheal tug and paralysis of the left recurrent laryngeal nerve were present. X-ray examination showed only a dilated aorta and cardiac enlargement. He believed that these signs could be explained only by the presence of an aneurysm compressing the pulmonary artery. From his electrocardiographic studies he concluded that there was also a block of the "left branch of Tawara's node." One electrocardiogram was illustrated with the interpretation of which we disagree. It does not appear to us to fulfill the criteria necessary for a diagnosis of bundle-branch block but rather indicates marked right axis deviation which could be explained easily by pulmonary stenosis with right ventricular hypertrophy. At autopsy an aneurysm the size of a walnut was found. It projected into the pulmonary artery causing high degree stenosis but in view of its size it appeared to be situated too high up to have damaged the septum. The aorta showed signs of lues and was dilated while the aortic valve was incompetent. The description of the studies of the bundle appear too vague to permit definite conclusions.

The case which we are reporting was studied thoroughly both clinically and by x-ray but aortic aneurysm was not suspected, as there was no evidence on which such a diagnosis could be supported. As there was no rupture the characteristic physical signs of communication between the aorta and the pulmonary artery or right ventricle were lacking. The

rough systolic murmur heard best in the second left interspace and the marked globular shape of the right heart on x-ray lead us to suspect that a lesion of the aortic valve did not cover the complete diagnosis and congenital pulmonary stenosis was considered an additional possibility. At autopsy, stenosis of the pulmonary artery and conus, due to compression by the aneurysm, was found and incompetence of the pulmonary valve had been produced. It seems probable, in view of the relatively slight change in the aortic valve and the paucity of peripheral signs of aortic insufficiency, that the diastolic murmur was really due to pulmonary incompetence.

The electrocardiographic findings were of considerable interest in that the tracings showed partial bundle-branch block in which the chief initial deflection was downward in Lead I and upward in Lead III. For many years, based on the experimental work of Lewis and his associates,<sup>10, 11</sup> this was considered to represent a lesion of the left division of the bundle of His. Fahr,<sup>12</sup> on theoretical grounds, called in question this interpretation and believed that the curves ascribed to right bundle-branch block by Lewis were really curves of left bundle-branch block and vice versa. Barker, Macleod, and Alexander,<sup>13</sup> as a result of their study of extrasystoles in the exposed human heart, brought forward evidence which strongly supported the latter view and, more recently, other workers, both on theoretical<sup>14, 15</sup> and experimental<sup>16, 17</sup> grounds, have come to the same conclusion. The present case cannot furnish conclusive evidence on this point as extensive necrosis of the septum was found and the divisions of the bundle could not be traced by serial sections. However, the facts that the aneurysm projected into the right ventricle and that the damage to the septum was greater on the right side make it probable that the right, rather than the left division of the bundle was damaged, thus tending to support the newer conception. Also, assuming that the bundle of His pursued its normal path, the point of penetration of the septum and subsequent course of the left division would be below and posterior to the aneurysm, while the region traversed by the right division in its course to the papillary muscle would be invaded by the lower pole of the aneurysmal sac.

Several causative factors appeared to be concerned in the extensive damage to the septum. The aneurysm, pushing downward into the base of the septum, caused considerable atrophy and fibrosis in the subjacent tissue. There were also a number of small gummata and extensive areas of recent necrosis. Although the main branches of the coronary vessels showed no evidence of thrombosis, they were markedly compressed where they skirted the aneurysm. Some of the degenerative myocardial changes might be ascribed to this compression with resulting restriction of the blood supply. This must at least have played an important part in the cardiac decompensation.

## SUMMARY

A case is reported of a patient suffering from luetic aortitis in whom an aneurysm 9 cm. in diameter, arising in the first portion of the ascending aorta, had produced none of the usual clinical evidences of aortic aneurysm. A high grade bundle-branch block was known to have been present for a period of eleven months prior to death from myocardial failure. The aneurysm, which had not ruptured, caused a marked stenosis of the pulmonary artery and insufficiency of the pulmonary valve. It projected into the right ventricle and produced considerable damage to the interventricular septum. This appeared to be the most important factor in the causation of the bundle-branch block. Slight aortic insufficiency was also present.

We wish to thank Dr. Alfred E. Cohn for his assistance in the study of the bundle of His.

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# BRAIN ABSCESS (PARADOXICAL) IN CONGENITAL HEART DISEASE\*

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ALTHOUGH the older English students recognized cerebral abscess as part of the classic picture of congenital heart disease,<sup>1</sup> nevertheless relatively few cases, confirmed by postmortem examination, have been reported since Ballet<sup>2</sup> in 1880 first definitely assumed a causal connection between this cerebral lesion and congenital cardiac conditions. Abbott, Lewis and Beattie<sup>1</sup> in 1923, after a careful search of the literature collected 14 cases of paradoxical cerebral embolism, 6 of which proved to be cerebral abscesses. We have been able to find only 4 additional cases reported up to the present time. We wish therefore to record this case which we had the opportunity of observing.

## CASE REPORT

T. S. (Case No. 124623), female, aged sixteen and one-half years, Hebrew, school-girl, was seen in consultation at her home on November 24, 1929 by one of us (M. A. R.) who, because of the story of a sudden onset of cerebral symptoms, fever, and the presence of a congenital cardiac lesion, made the diagnosis of a paradoxical brain abscess, and sent her into the wards of the Jewish Hospital of Brooklyn, where the following history was recorded. Her chief complaints at the time of admission were headache and vomiting of one week's duration. Her family history was essentially negative. Her past history revealed measles during infancy, tonsillectomy at the age of seven, and the fact that it was known that she had had a cardiac lesion since infancy. There was no history of cyanosis, episodes of cardiac failure, or embolic phenomena. The patient was apparently well until one week before admission, when, following a large and indigestible meal she became ill with abdominal discomfort and malaise. The next morning she awoke with a severe generalized headache which became associated on the following day with vomiting, not projectile in character, and often induced by the patient. The headache grew progressively worse, and at the time of admission to the hospital was localized occipitally and described as "terrific and unbearable." There was no history of fever, sweats, convulsions, twitchings, or paralyses.

Physical examination revealed a female of about sixteen years of age, well nourished and developed, acutely ill, very restless, thrashing about in bed, face flushed, lips cyanotic. The scalp was normal. Tenderness was elicited over the occipital region. The eye examination revealed the nasal half of the right disc to be blurred and indistinct, the temporal half showing beginning blurring, and a swelling of the disc of one diopter; the left disc showed a swelling of 3 diopters; the veins were distended and tortuous; there were no hemorrhages or exudate. The ears and nose were negative. The tongue protruded in the midline. The teeth were in good condition. There was no rigidity of the neck. Percussion of the heart showed enlargement to the left. There was a rough systolic murmur most marked at the apex, but heard over the entire precordium and at the base. The sounds were of good quality and regular in rhythm. The abdomen revealed no tenderness or masses, the liver and spleen were not felt. The extremities were negative, except for cyanosis

\*From the Medical Service of the Jewish Hospital of Brooklyn.



of the finger tips and toes. The deep reflexes of the upper extremities were sluggish. The abdominal reflexes were sluggish; the knee jerks very sluggish; the ankle jerks active. The Brudzinski and Kernig signs were negative. The Babinski and Hoffmann signs were bilaterally positive.

On admission the temperature was 99.4° F., pulse 86, respirations 20. The white blood cell count showed 17,100 leucocytes, 88 per cent polymorphonuclears, 4 per cent mononuclears and 8 per cent large lymphocytes. The red cell count was 6,120,000 with 100 per cent hemoglobin. The blood pressure was 100 mm. systolic and 70 diastolic. Spinal puncture revealed fluid under markedly increased pressure, with 20 lymphocytes per c. mm., and chemical examination showed sugar 93 mg. per 100 c.c., albumin 4 plus, globulin 3 plus; no tubercle bacilli were found. The colloidal gold curve was 00001333220. The blood Wassermann and Kahn reactions were negative.

The patient was admitted to the hospital at 9:30 P.M. She received magnesium sulphate solution intramuscularly and 50 per cent glucose intravenously. She appeared quieter and more comfortable, but died suddenly at 7 A.M. the next day.

*Postmortem Examination.*—General: Body was that of a well-developed and well-nourished female about sixteen years of age.

Cavities showed no abnormalities.

Lungs were voluminous. On section there oozed from the cut surface a large amount of bluish red frothy material. Throughout the parenchyma were scattered many hemorrhagic areas about 4 mm. in diameter. The bronchi and vessels appeared normal. Microscopically the lung tissue was markedly congested, and edematous. The alveoli contained numerous red blood cells.

Heart weighed 340 grams, was pointed and contracted. The surface was dull and the pericardium was opaque in spots. The right auricle was normal. The foramen ovale contained two funnel-shaped openings. The right ventricle was enormously thickened, the wall measuring about 1 cm. The accessory musculature was hypertrophied. The tricuspid valve was normal. The left auricle was normal in size. The wall of the left ventricle was about 4 mm. thick and appeared normal. The mitral valve was normal. The septum membranacea and the upper portion of the intraventricular septum were missing. The upper border of the septum was represented by a semilunar rim with a concavity facing upward. The aorta originated from the right, while the pulmonary artery arose from the left side of the common ventricular orifice. The pulmonary ostium was decidedly smaller than normal. The ductus arteriosus was not patent. The aortic and pulmonary valves were normal.

Esophagus and stomach showed some submucous hemorrhages.

Intestines appeared normal. The papilla of Vater was patent.

Pancreas weighed 79 grams and appeared normal, macroscopically and microscopically.

Spleen weighed 118 grams. Capsule was smooth, color was deep purple, consistency normal. On section parenchyma was deep blue in color, the follicles were large and prominent. On the anterior perirenal tissue there was found an accessory spleen, 1.5 cm. in diameter, resembling on section the splenic tissue. Microscopically the spleen and accessory spleen showed congestion and hemorrhage in the pulp with endothelial hyperplasia.

Adrenals weighed 13 grams each, and showed no abnormalities. Microscopic examination revealed an adenoma.

Kidneys weighed 107 and 122 grams. They were normal in size and shape. Capsule stripped easily, leaving a smooth, clean surface. On section they appeared normal except for a deep blue red appearance. Microscopic examination showed congestion and extensive hemorrhages in the collecting tubules.

Ureters and bladder were normal.

Uterus was soft, slightly enlarged. Mucosa was thick and red (menstrual). Microscopic examination of ovaries and uterus showed them to be normal.

Bone marrow was normal.

Liver weighed 1300 grams; on microscopic examination it appeared normal.

The ears and sinuses were normal. The calvarium contained a number of thin areas of varying size through which light passed (osteogenesis imperfecta).

Brain weighed 1275 grams. Dura was normal. The entire brain was markedly edematous, the right side more than the left. The convolutions were very prominent. The optic nerves appeared flattened. In the cerebellum there was an abscess cavity, of the size of a walnut, containing foul smelling pus. On culture this pus showed *Bacillus coli*. The membranes were normal. The pituitary body was microscopically normal.

The findings in the heart in this case on postmortem examination present the typical combination of congenital cardiac anomalies known as the "Tetralogy of Fallot,"<sup>3</sup> namely pulmonary stenosis, ventricular septal defect, dextroposition of the aorta and hypertrophy of the right ventricle. Although, as was brought out by Baumgartner and Abbott,<sup>4</sup> this is the most common of all cardiac abnormalities in patients with congenital cyanosis reaching adult life, this patient gave no previous history of cyanosis or signs of cardiac embarrassment.

The source of the infected embolus is not clear in this case. The onset of the illness with gastro-intestinal symptoms and the finding of foul smelling pus in the cerebellar abscess cavity, which showed the colon bacillus on culture, suggest the possibility of the gastro-intestinal tract as the point of origin.

#### DISCUSSION

The history of the study of the mechanism of the paradoxical brain abscess applies of course also to the paradoxical embolus without the infective factor. Abbott, Lewis, and Beattie<sup>1</sup> reviewed the work of Cohnheim (1877) who was the first definitely to trace the path of an embolus through an opening in the cardiac septum, and whose findings were later confirmed by Virchow (1880), Zahn<sup>5</sup> (1881), Rostan<sup>6</sup> (1884), and Hauser<sup>7</sup> (1888). Ohm<sup>8</sup> in 1907 reported a case of hemorrhoidal vein thrombosis which gave rise to repeated cerebral emboli in a case of patent foramen ovale. He discussed in detail the mechanism involved.

The brain abscess is the result of a primarily infected embolus or, less frequently, of secondary infection after embolization has occurred.

While we find the occurrence of the paradoxical cerebral abscess most often in the congenital cardiac patient presenting the combination known as the "Tetralogy of Fallot," the occurrence is possible in any case where a communication exists between the right and left sides of the heart. Baumgartner and Abbott<sup>4</sup> report a case occurring with a much less common combination of congenital cardiac anomalies, known as the "Eisenmenger complex," described by Abbott,<sup>9</sup> which differs from the "Tetralogy of Fallot" in that there exists a dilatation instead of a stenosis of the pulmonary artery. Ballet's case<sup>2</sup> presented only the interventricular septal defect without the other anomalies of the

"tetralogy." Ballet quoted the case of Lallemand in which there was a patent foramen ovale, pulmonary stenosis, and no ventricular septal defect.

The 10 cases which we have reviewed are classified according to the cardiac anomalies which existed and summarized as follows:

#### I. DEFECT OF THE INTERVENTRICULAR SEPTUM

##### *A. Resembling the "Tetralogy of Fallot."*

1. By J. R. Farre<sup>10</sup> (1814). Male, aged nine and one-half years. Cyanosis observed definitely from the age of two and one-half. Four days before death, left hemiplegia, with severe pains in head, fever, and rapid pulse rate. Autopsy findings: Ventricular septum defect, pulmonary stenosis, deviation of aorta to the right. Abscess in right hemisphere of brain, containing one-half ounce of thick pus.

2. By Charles Bertody<sup>11</sup> (1845). Female, aged twenty-one years, complained of slight cyanosis and dyspnea on exertion through life. Always suffered from headaches, which a few days before death became markedly increased and were associated with fever and later with delirium and coma. Autopsy findings: Ventricular septum defect at orifice of aorta. Pulmonary artery contracted and aorta arising from both ventricles. Abscess in left posterior lobe of brain, size of a pigeon's egg; left lateral ventricle filled with pus.

3. By W. H. Stone<sup>12</sup> (1881). Female, nineteen years old. Cyanosis and dyspnea from birth. Sudden onset of severe headache shortly before death. Autopsy findings: Conus stenosis of right ventricle; acute endocarditis of lower conus orifice. Large ventricular septum defect at base below aortic orifice. Right ventricular wall hypertrophy. Purulent meningitis. Cerebral abscess in right occipital lobe, containing fetid pus, which had burst into the horn of the right lateral ventricle.

4. By Th. Deneke<sup>13</sup> (1906). Male, aged eighteen years. Cyanosis and clubbing of fingers since childhood. Ten days before death sudden onset of severe headaches and left-sided hemiplegia. Autopsy findings: Large ventricular septum defect. Transposition of aorta and narrowed pulmonary artery. Right ventricular hypertrophy. Narrow ductus Botalli. Streptococcal abscess of right cerebral hemisphere, size of walnut.

5. By Abbott, Lewis and Beattie<sup>1</sup> (1923). Male, aged eleven years. Cyanosis and dyspnea from birth. Appendectomy for acute appendicitis eight days before death. Six days after appendectomy sudden onset of severe headache and temperature of 101° F. On following day right hemiplegia. Autopsy findings: Pulmonary atresia, ventricular septum defect at base. Aorta arising from conus of right ventricle. Hypertrophied right ventricle. Cerebral abscess of left frontal lobe. Purulent meningitis.

6. By William Raab<sup>14</sup> (1923). Male, aged fifteen years. Cyanosis and dyspnea since attack of scarlet fever at age of six. Sudden onset of violent frontal headaches and fever to 104° F. three weeks before death. One week before death, left hemiplegia. Autopsy findings: Hypoplasia of pulmonary artery with stenosis of orifice. Ventricular septum defect, patent foramen ovale. Right ventricular hypertrophy. Aorta arising from both ventricles. Recrudescing verrucous endocarditis of all valves of all orifices. Abscess, size of hen's egg, in right cerebral hemisphere under central fissure, and perforation of abscess into right lateral ventricle. Purulent meningitis.

7. By Frances Bach<sup>15</sup> (1928). Male, aged thirty years. Dyspnea and cyanosis since birth. For ten years fainting spells and severe frontal headaches on exertion. Fourteen days before death 6 carious teeth were removed. Five days later onset of severe frontal and temporal headaches. Temperature to 103° F. Headaches progressive. Coma. Autopsy findings: Tooth sockets healthy. Heart: Aorta arising from both ventricles; narrowed pulmonary artery; hypertrophied right ventricle; large

ventricular septum defect; open foramen ovale. Brain: Large abscess in right posterior temporal region; purulent meningitis.

*B. Presenting the "Eisenmenger Complex."*

8. By Baumgartner and Abbott<sup>4</sup> (1929). Male, aged twenty years. Moderate dyspnea and cyanosis on exertion all his life. About two weeks before death onset of headache. Later drowsiness, left hemiplegia, difficulty in speech, progressive headache, coma. Autopsy findings: Marked dilatation of pulmonary artery, aorta arose from both ventricles, ventricular septum defect, right ventricular hypertrophy. Large abscess in right frontoparietal region involving motor area and internal capsule. Culture of pus showed *Streptococcus hemolyticus*.

*C. Ventricular Septum Defect With Anomalies Other Than the Above.*

9. By Ballet<sup>2</sup> (1880). Male, aged fifteen years. No history of cyanosis. Left hemiplegia ten days before death. Autopsy findings: Ventricular septum defect. Malposed septum. Aplastic right ventricle. Both auricles opened into left ventricle which was markedly hypertrophied. Abscess, size of small orange, in frontal lobe, and purulent infiltration of surrounding brain tissue.

II. PATENT FORAMEN OVALE WITH PULMONARY STENOSIS AND CLOSED INTERVENTRICULAR SEPTUM

10. By Lallemand<sup>10</sup> (1821) (quoted by Ballet). Female, aged fifty-seven years. Violet-red color of face since infancy. Severe dyspnea on exertion. Left hemiplegia, twelve days before death. Autopsy findings: Patent foramen ovale, pulmonary artery stenosis, right auricular and right ventricular hypertrophy. Cerebral abscess, size of hen's egg, in right hemisphere containing 3 ounces of yellowish-green pus.

That the condition is more common than the paucity of the subject in the literature would lead one to believe is indicated by an analysis of 711 consecutive autopsies by Rostan.<sup>6</sup> He found a patent foramen ovale 139 times, or in 20 per cent of the cases; and in 7, or 5 per cent, of these, paradoxical embolism had taken place, and in 3 of the 7 cases it was cerebral. And, as was brought out by Baumgartner and Abbott,<sup>4</sup> and observed in this collected series of cases, termination by brain abscess is especially liable to occur in ventricular septal defect, particularly so when there is dextroposition of the aorta, such as occurs in the "Tetralogy of Fallot," for then there is a more direct path for the transmission of the infected embolus.

The paradoxical brain abscess seems to occur somewhat more frequently in males than in females, the ratio in this series being 7 males to 4 females. The case with open foramen ovale and closed ventricular septum was in a female who had reached the age of fifty-seven; but the cases with ventricular septal defect all occurred at a comparatively early age. The age of the patients varied from nine and one-half to thirty years, the average being sixteen and one-half years. The source of the infected embolus cannot often be determined. In Case 5 it occurred after operation for acute appendicitis; in Case 7 it probably was due to the extraction of carious teeth; in the other cases the source was less definite. There does not appear to be any particular site of predilection in the brain for the occurrence of the abscess. Ours was the only case in which it occurred in the cerebellum.

The symptoms of paradoxical brain abscess do not differ essentially from the symptoms of brain abscess of any other source. The local signs and symptoms are the most important. Fever and a leucocytosis may be present. Eyeground examination and lumbar puncture may help in the diagnosis, depending on the location and size of the abscess.

#### SUMMARY

A congenital cardiac case presenting the combination known as the "Tetralogy of Fallot" and terminating with a paradoxical cerebellar abscess is reported, and a review from the literature of ten additional cases of paradoxical brain abscess is discussed. The sudden onset of cerebral symptoms in congenital cardiac cases, where interauricular or interventricular septal defects are suspected should lead one to consider a diagnosis of paradoxical brain abscess regardless of whether a septic focus can or cannot be demonstrated. On the other hand, the presence of an idiopathic brain abscess should lead one to suspect the possibility of the presence of a congenital cardiac anomaly.

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# A LIGHT WEIGHT PORTABLE ELECTROCARDIOGRAPH

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THE clinical use of the electrocardiograph has been hampered by the excessive weight and bulk of the present so-called portable instruments, and also by the fact that the records taken by these portable instruments differ in many respects from the records taken with the standard string galvanometer. These defects of excessive weight and unsatisfactory recording are not inherent in portable electrocardiographs but can readily be eliminated by proper care in design and construction. The truth of this statement can be judged from the following description of a portable electrocardiograph which has been so constructed as to combine a maximum of serviceability with a minimum of inconvenience.

The characteristics of this instrument are as follows:



Fig. 1.

1. The total weight is forty-three pounds complete with batteries in two metal boxes which measure 7 by 9 by 11 and 7 by 9 by 18 inches respectively.

2. The record taken is of standard width (6 centimeters). It may be recorded on either film or paper. It is a replica of the record taken with the standard string galvanometer.

3. The instrument operates from its own batteries and is independent of the house current.

4. Durability and accuracy have been tested by frequent use for the past nineteen months.

Fig. 1 shows a record taken with this instrument.

The instrument operates by means of a three stage amplifier of simple construction, using standard tubes obtained in the open market. This amplifier has been especially designed to avoid distortion. The accurate amplification of the QRS complex is comparatively simple but the T-waves present special difficulties and special attention was paid to them in the design, with the result that the slowest

T-waves are amplified without appreciable distortion. This is indicated by the fact that if a constant voltage is applied to the input of the amplifier (see Fig. 1) the record shows a deflection which is practically horizontal for over one-fifth of a second.

The galvanometer, which is of the moving mirror type, has a natural period considerably shorter than  $1/100$  of a second. It is critically damped so that it can be very quick without overshooting under any conditions. This galvanometer reflects a very wide beam of light in the center of which is the shadow of a wire, thus duplicating the picture produced by a string galvanometer and permitting the use of a time marker of simple construction.

The apparatus is made mostly of duralumin and aluminum; no structural parts are made of wood. Thus it is rugged and rigid, and it cannot warp out of shape with changes of climate. A single electric motor operates the camera and the time marker. Its speed is accurately controlled by a special speed control which can be relied upon within a fraction of one per cent. The batteries used are Edison alkali batteries which have a long life and do not give off corrosive fumes.

The amplifier box contains the amplifier with its batteries and a control panel. This panel carries a main battery switch, a filament rheostat, a voltmeter indicating both high and low voltage, a lead selector, and a switch for applying a millivolt, used in standardizing the instrument. A three conductor cord goes to the patient, and a two conductor cord is plugged into the camera box.

The camera box contains the galvanometer and optical system, the film, the time marker, the driving mechanism and its storage battery, and a control panel. The control panel carries a jack to receive the amplifier plug, a knob to adjust the light beam position, a knob to adjust sensitivity, a switch to turn on the light and motor, and a periscope to view the heart action during operation.

In contrast to the string galvanometer the sensitivity of this electrocardiograph is not affected by skin resistance, and adjusting the sensitivity does not involve changing the speed of deflection. It can be operated in broad daylight.

It is to be emphasized that the light weight and other desirable characteristics of this instrument have been achieved solely through careful design and without the sacrifice of any essential parts. Its construction has involved great care to make the instrument not only portable but durable. And finally, the construction of this electrocardiograph has involved a far smaller financial outlay than would have been involved in the purchase of any of the available commercial electrocardiographs.

## PORTABLE ELECTROCARDIOGRAPH GIVING DIRECT INK TRACINGS\*

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MANY attempts have been made to record *mechanically* the action currents of the human heart by means of vacuum tube amplifiers. The difficulties are considerable, owing to the weakness and low frequency of the electrocardiac current.

Different types of amplifiers have been employed, but they have all proved insufficient to give a faithful record of the electrocardiograms.

The great clinical interest attached to this problem in medical practice induced us to make further attempts. By the use of the "ticker" we have been able to surmount the difficulties arising from the natural form of biological currents.

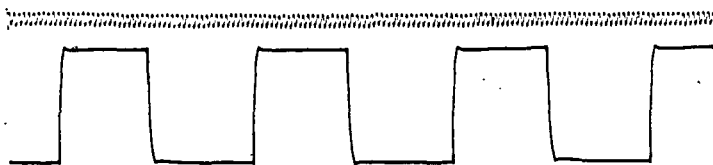


Fig. 1.—Record of a current of 1 millivolt. Timing 1/50 sec.

The ticker is an interrupter which has been used primarily in wireless telegraphy for the purpose of audition. Its application to the amplification of action currents has given us entire satisfaction.

The ticker in combination with an amplifier increases the intensity of action currents of the heart to such an extent as to set in motion a mechanical writing oscillograph. This oscillograph is an electrodynamic arrangement specially designed for this purpose by us. It consists essentially of a moving coil to which is attached a glass pen which records in ink the tracings on ruled paper. The ink supply is derived from a special container which prevents overflowing during transport.

The maximum range of the pen on the paper is 6 cm. and the maximum periodicity 100 per sec.

Special arrangements are provided to prevent overshock of the moving pen. The tracing in Fig. 1 shows the efficacy of this contrivance.

The amplifier and the oscillograph are under complete electrical and mechanical control. Figs. 2 and 3 effectively demonstrate this point, and show at the same time the similarity of the curves obtained by an optical standardized electrocardiograph (Boulitte) and our direct ink tracing method.

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At the same time these curves prove the accuracy of the electrocardiographic systems with amplifier, which are not inferior to the string galvanometers.

The sensibility of our electrocardiograph is regulated by the degree of amplification, whereas in the optical systems it is regulated by the tension of the string. The tension of the steel wires which support the moving coil in our electrodynamic oscillograph is constant, and this fact

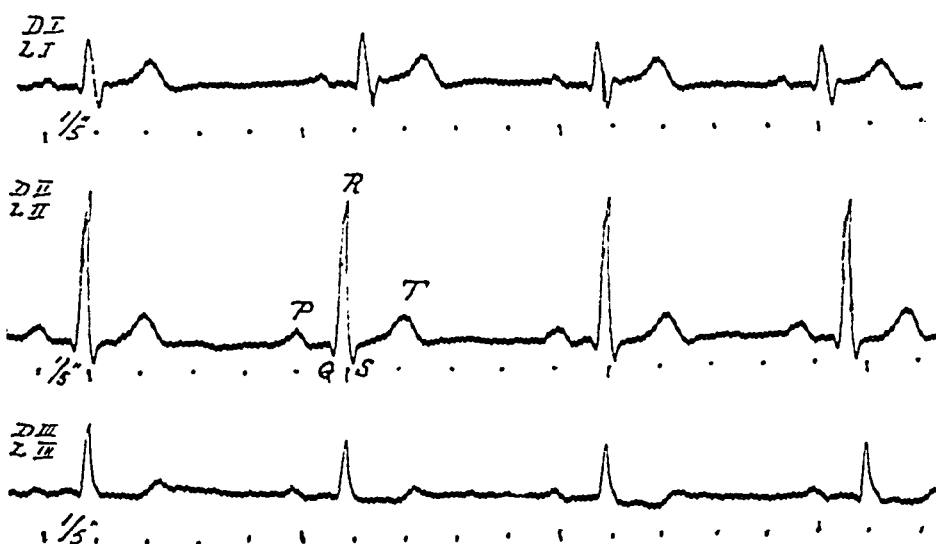
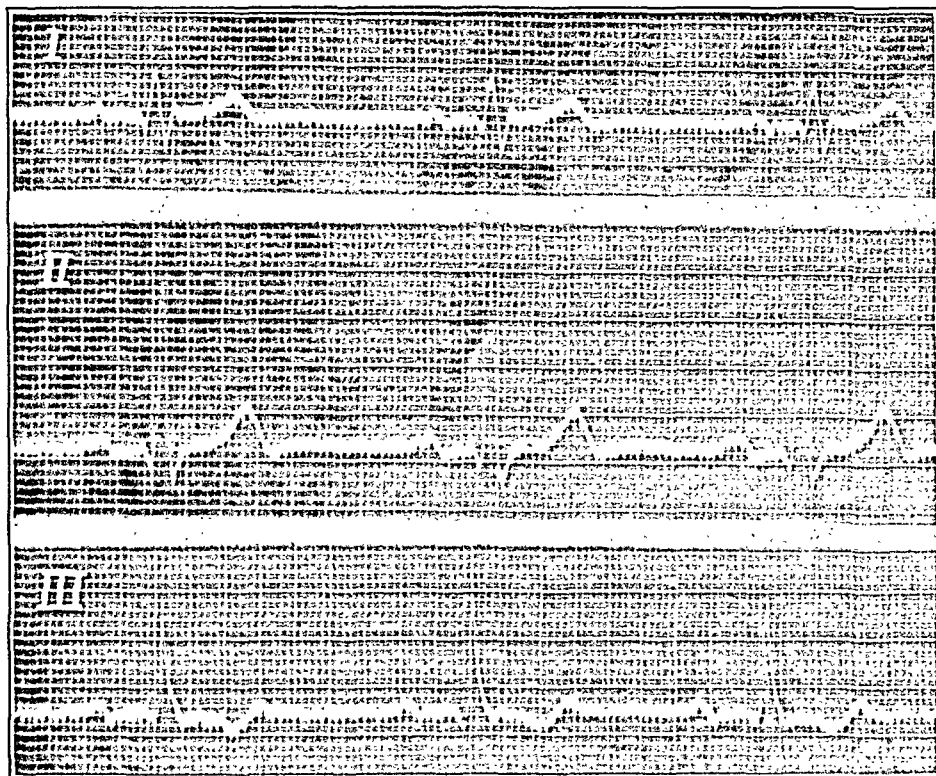


Fig. 2.—Normal case. The same electrocardiogram taken with an optical standardized apparatus (Boulitte) and the direct ink tracing electrocardiograph. (Natural size.)

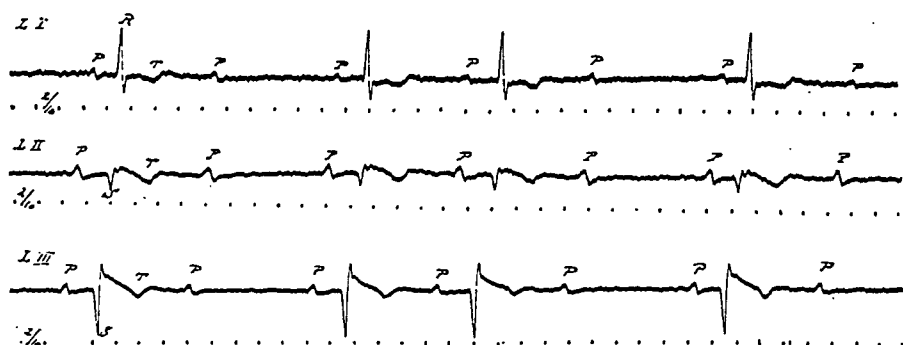
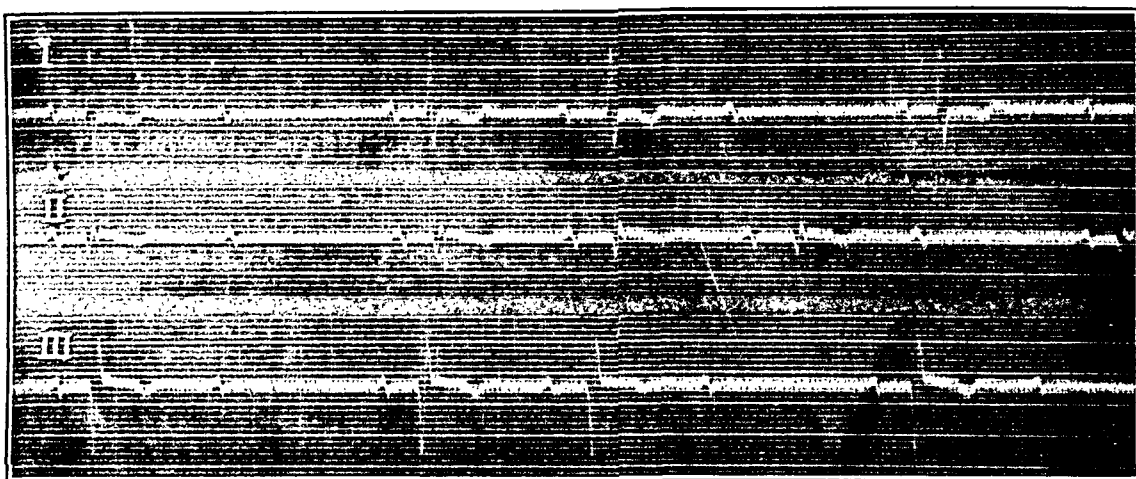


Fig. 3.—Myocardial infarction. Electrocardiograms taken at the same time with the optical method and the direct ink tracing apparatus (eight days after a severe attack). Auriculo-ventricular block, typical T-wave. (Reduced  $1/3$ .)

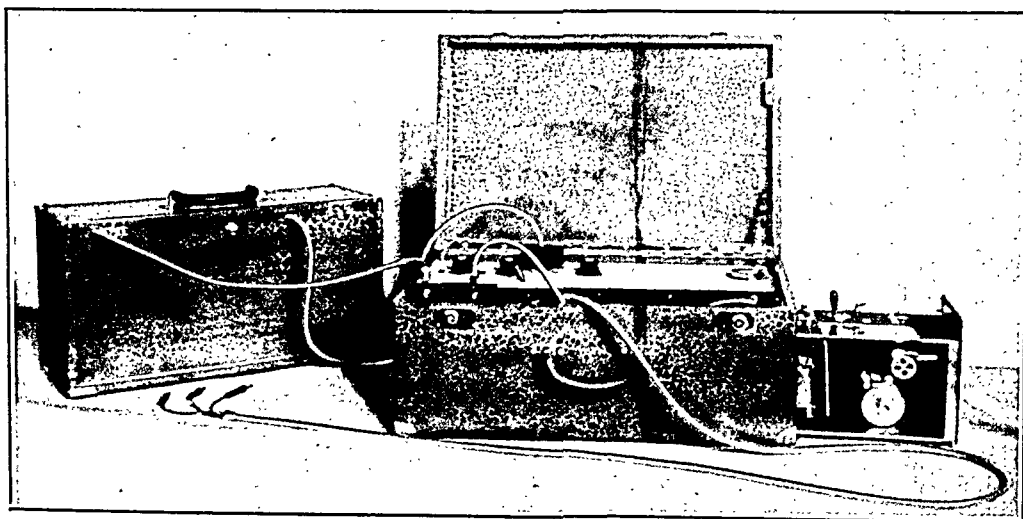


Fig. 4.—Portable electrocardiograph giving direct ink tracings. To the right one sees the oscillograph with its writing pen and the tracing issuing from the box.

guaranties the regularity of the curves independently of the resistance of the patient under examination.

In addition, Figs. 2 and 3 show that the ink tracings are not inferior to the photographic tracings in the precision of the waves or the neatness of the curve.

Our portable direct ink tracing electrocardiograph consists of the two neat cases whose total weight is 37 kilograms (Fig. 4). One case contains the accumulators and the other the electrocardiograph. By means of this apparatus the physician is able to obtain a complete electrocardiogram by the bedside of the patient in less than ten minutes.

Our object in presenting this apparatus to medical practitioners is twofold: first, the great simplicity in its application, and second, the advantage of having an exact tracing on the spot.

## Department of Clinical Reports

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### SUBACUTE BACTERIAL (*STREPTOCOCCUS VIRIDANS*) ENDOCARDITIS AND ENDARTERITIS INVOLVING THE TRICUSPID VALVE AND THE PULMONARY ARTERY IN A UNIQUE CASE OF THE TETRALOGY OF FALLOT COMPLICATED BY CONGENITAL PULMONARY REGURGITATION

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THE termination of life in congenital cardiovascular disease by the complication of subacute bacterial (*Streptococcus viridans*) endocarditis and endarteritis is not rare. Maude Abbott<sup>1</sup> reports that among 555 cases of congenital cardiac disease analyzed by herself, 98 (or 17.6 per cent) presented such subacute bacterial invasion. Of 82 of these cases, 20 (or 23 per cent) were cyanotic patients with pulmonary stenosis, made up almost wholly, in all probability, of instances of the tetralogy of Fallot (pulmonary or infundibular stenosis, interventricular septal defect, dextroposition of the aorta, and right ventricular enlargement). An analysis from the opposite point of view by Abbott on the same page reports that among 84 patients with pulmonary stenosis and ventricular septal defect there were 25 cases (30 per cent) of acute or subacute endocarditis. Examples of the complication of subacute bacterial endocarditis and pulmonary endarteritis in the tetralogy of Fallot have been published by Abbott<sup>3</sup> and by Leadingham.<sup>4</sup> Involvement of the pulmonary artery by subacute bacterial infection has been discussed by a number of authors, including Mehlin<sup>5</sup> and Gordon and Perla;<sup>6</sup> the majority of such cases show patency of the ductus arteriosus.

We have obtained postmortem examinations in three of our private patients with the tetralogy of Fallot. The first two patients died of heart failure, complicated by cerebral symptoms, and of apoplexy respectively, at the ages of twenty-three and of sixty years. The third case, which forms the basis of the present report, was a young woman aged twenty-one years who died of subacute bacterial (*Streptococcus viridans*) infection involving the tricuspid valve and the pulmonary artery. Her heart was especially remarkable in that it showed in addition to the tetralogy of Fallot a congenital defect in the pulmonary valve itself, giving rise to pulmonary regurgitation, which lesion rendered the exact diagnosis clinically a difficult one. Congenital pulmonary regurgitation is very rare, having been noted only 12 times in Maude Abbott's series of 1000 cases,<sup>2</sup> but we ourselves happen to have

found the condition once before at postmortem examination,<sup>7</sup> and in that case the cusps were entirely missing.

The present case is reported, therefore, partly because of its rarity and partly to throw light on the establishment of the correct diagnosis of pulmonary regurgitation in similar cases in the future.

#### CASE REPORT

W. H. M., a young woman student, aged twenty-one years, entered the Baker Memorial Hospital (Massachusetts General Hospital) on April 8, 1930, with a history of an acute illness of six weeks' duration. Trouble started with a "cold in the head" and fever. There was a coryza for a few days only but the fever persisted. Diarrhea came on after the head cold had subsided, and for several weeks there were three to four watery movements a day without pain and without blood or mucus in the stools. Gradually the diarrhea subsided but the stools were still abnormally frequent and loose on admission to the hospital. Her diet had consisted mostly of buttermilk for the first part of the illness but was changed later to a light mixed diet. For two weeks before entrance to the hospital a mild cough had existed.

Her past history revealed one important point. At the age of five years, in 1914, she had been examined by a pediatrician for some minor complaint and a harsh systolic murmur with palpable thrill had been found in the pulmonary valve area. In 1916 there were the same findings along with a suspicion of active endocarditis. She was sent to a children's heart hospital for a few weeks and discharged in good condition. At the age of nine years in 1918 she had her tonsils and adenoids removed. On repeated examinations, the last of which was in 1924, the heart is said to have shown what it did at first. After long continued observation over a period of ten years which included the finding of slight transient cyanosis on exertion, a final diagnosis of some kind of congenital heart disease was made by the pediatrician who had seen her first in 1914. The only infections in childhood were measles and chickenpox. There was no history of scarlet fever, rheumatic fever, diphtheria, or pneumonia.

The family history was good. Father, mother, one brother, and one sister were living and well.

*Physical examination* on April 8, 1930, on admission to the hospital, showed a young woman lying comfortably, flat in bed with slight but definite cyanosis of the lips and toes but little or no clubbing of either fingers or toes. There was no dyspnea. No petechial hemorrhages or nodules were found anywhere over the body. The heart showed slight enlargement, the apex impulse and left border of dullness being found in the fifth intercostal space 9.5 cm. to the left of the midsternal line and 1.5 cm. beyond the midclavicular line. The heart sounds were normal. There was a loud harsh systolic murmur heard best at the left of the upper sternum in the second and third interspaces and not well heard elsewhere over the precordium. It was attended by a palpable thrill. There was also heard a slight but definite blowing early diastolic murmur at the left of the upper sternum maximal in the second space. The two murmurs were not continuous but were distinctly separated from one another. The lungs were clear but showed harsh breath sounds throughout. The abdomen was normal. Liver and spleen were not palpable. There was no edema over back or legs.

At this time, before further study was made, the following comments were written in the record: "The diagnosis is very difficult. The positive findings indicate infection and heart disease. Whether these two are now related is the question to determine. The heart condition suggests strongly a very unusual pulmonary valve

lesion, perhaps congenital (that is, pulmonary stenosis), perhaps acquired (pulmonary stenosis and regurgitation) or perhaps combined (that is, subacute bacterial endocarditis complicating a congenital lesion). There does not seem to be definite evidence of mitral or aortic disease. *Treatment.* Symptomatic therapy and continued study as to the cause of the fever and diagnosis as to heart lesion. *Probable diagnosis:* Subacute bacterial endocarditis involving the pulmonary valve, perhaps superimposed on congenital pulmonary stenosis. Bacterial endocarditis complicating congenital patency of the ductus arteriosus is the other possibility."

On April 10, 1930, the following note was made: "The character of the murmurs in the pulmonary valve area is not typical of patent ductus arteriosus. The time of the loudest murmur and thrill is systolic. Pulse is not Corrigan."

On April 11, "Fluoroscopic examination shows marked prominence and bulging in the region of the pulmonary artery with vigorous pulsation, appearing to be a Corrigan pulse in the pulmonary artery. There is also well marked pulsation of the lung hiluses. Heart somewhat enlarged.

"Electrocardiogram shows normal rhythm, rate 105, slight to moderate right axis deviation, but not typical of marked congenital pulmonary stenosis."

On April 14, "The report of a positive blood culture confirms the diagnosis of bacterial endocarditis."

On April 18, "Spleen not palpable. Condition shows no appreciable change. Murmurs as before. No petechial hemorrhages or evidence of embolism."

Dr. Maude E. Abbott saw this patient in consultation on April 18 and made the following note: "Tentative diagnosis—Patent ductus arteriosus with dilatation of the pulmonary artery and infective pulmonary endarteritis, beginning around the pulmonary orifice of the ductus arteriosus, probably extending down to and involving the pulmonary valve with pulmonary insufficiency from destruction of the cusps." Our own note that same day follows: "This diagnosis by Dr. Maude Abbott is very logical and seems likely to be correct. There is no specific therapy and the prognosis is bad. It is probably a matter of a few weeks."

On April 26 she was discharged from the hospital with the following note: "There has been no appreciable change in her condition since entrance except for a moderate increase in the secondary anemia and the development of slight clubbing of the fingers. It is probable that there will be some weeks or even months before the termination of this illness. The prognosis is hopeless." The diagnosis on discharge was: "Congenital patency of the ductus arteriosus with subacute bacterial endocarditis and endarteritis, involving the ductus arteriosus, pulmonary artery, and pulmonary valve. *Streptococcus viridans* is the causative agent of the endocarditis."

During the next two months this patient gradually failed at home and died on June 25, 1930, having had "acute meningeal symptoms for the last day or two." The known duration of the illness was four months.

#### LABORATORY DATA DURING HOSPITAL STAY

The temperature chart showed constant fever, ranging from 99° to 104.5°, with daily swings from the lowest figures in the morning to the highest in the evening.

Urine, April 8, 1930. Normal, acid, specific gravity 1.014, very slight trace of albumin, no sugar, bile or pus. Sediment: occasional squamous cells, occasional leucocytes, few bacteria, rare red blood cells.

Blood counts and smears, April 9, 1930. White count 19,500, red count 4,450,000, Hgb. 70 per cent. Differential leucocyte count: 87 per cent polymorphonuclears, 8 per cent large lymphocytes, 4 per cent small lymphocytes, 1 per cent large mononuclears. Moderate achromia and marked polychromatophilia of red blood corpuscles with variation in size and shape. Platelets decreased.

April 18, 1930. White count 12,500, red count 3,650,000, Hgb. 55 per cent. Polymorphonuclears 83 per cent, small lymphocytes 13 per cent, mononuclears 2 per cent, unclassified 2 per cent. Slight achromia and slight variation in shape of red cells. Platelets slightly decreased in number.

Blood cultures April 9, 1930. Both flasks showed *Streptococcus viridans*.

April 15, 1930. 1. *Streptococcus viridans*. 2. *Streptococcus viridans*.

April 16, 1930. Both blood cultures showed *Streptococcus viridans*.

Electrocardiogram, April 9, 1930, showed normal rhythm, rate 105, and slight right axis deviation.

#### POSTMORTEM EXAMINATION, JUNE 25, 1930

The examination was performed eight hours after death, the thorax only being opened. There were slight cyanosis and a moderate clubbing of the fingers.

The lungs were moderately congested, and on the left the lower lobe was compressed and atelectatic, being displaced laterally and upward by an enlarged heart. The right lower lobe contained several small wedge-shaped areas, having the typical appearance of infarcts.

The heart weighed 540 grams. It was decidedly abnormal in shape, due in part to a dilatation of the right auricle, but principally to an hypertrophy of the right ventricle, producing a blunting of the apex, the whole organ assuming a roughly rectangular shape. The heart before removal from the chest was noted to lie almost at right angles to the midline.

The apex of the heart was made up practically entirely of right ventricle. Three-fourths of the anterior surface consisted of the right ventricle and one fourth of the left. The posterior surface was made up two-thirds of right ventricle and one-third of left ventricle.

The length of the heart from the base of the aorta to the apex was 11.5 cm., and from the superior vena caval opening to the apex, 15 cm. The anteroposterior thickness of the ventricles was 8 cm.

The pericardium was normal.

The chambers of the heart and the great vessels were in normal relationship. The venae cavae were normal and emptied into the right auricle. The latter was dilated to twice the normal size and its wall was slightly thickened. The foramen ovale was closed.

The tricuspid valve was slightly thickened, and on its cusps were many vegetations, most numerous on the posterior cusp where they consisted of long pedunculated grayish white masses, hanging down into the ventricular cavity, some measuring as much as 2.5 cm. in length. On the medial and anterior cusps there were a few shaggy vegetations only a few millimeters in length. The circumference of the valve was estimated to be 10 cm.

The right ventricle was dilated and markedly hypertrophied, being considerably larger than the left. The wall measured 12 mm. in thickness in the main cavity, thinning down to about 4 mm. in the pulmonary infundibulum. The muscle was of normal color and consistency. The infundibulum was 3 cm. in length and 22 mm. in diameter at its origin, narrowing gradually as it approached the pulmonary valve.

The pulmonary valve measured 15 mm. in diameter and was composed of two cusps, leaving when closed, a narrow slitlike opening  $14 \times 3$  mm. in size. One cusp extended the full diameter of the artery, and behind its free edge the shallow cup was divided into unequal portions by a narrow fibrous ridge extending from the free margin to the wall of the artery. The opposing cusp did not completely cover the other half of the artery, but left a small area 2 to 3 mm. in width on the anterior surface. This latter smaller cusp was more than twice as deep as the opposite one. There were no vegetations on the pulmonary valve.

The pulmonary artery was markedly dilated from the level of the valve to its first branches. About 3 cm. above the valve, it measured 9 cm. in circumference. On the external surface of the artery, beginning just above the level of the valve, and over an area about 4 cm. square, the wall was reddened, injected, roughened, and seemingly thinner than the remainder. On the intimal surface, corresponding to this area, the wall was covered with numerous shaggy vegetations, similar in appearance to those found on the tricuspid valve. The remainder of the pulmonary artery was negative except for the dilatation mentioned above. The ductus arteriosus was closed.

The left auricle was of normal size and thickness and contained no thrombi.

The mitral valve measured 8 cm. in circumference and except for a slight thickening of the cusps was normal in appearance. There were no vegetations on the valve.

The left ventricle, comprising less than one-half the bulk of the heart, was of normal size and not dilated. The muscular wall measured 11 mm. in thickness. The papillary muscles were not abnormal.

There was a defect in the interventricular septum measuring  $3 \times 1.5$  cm., 75 cm. above the apex of the left ventricle, and immediately below the dextroposed aortic valve.

The channel leading to the aorta from the left ventricle measured about  $2.5 \times 1$  cm., one side consisting of the aortic cusp of the mitral valve. In the right ventricle, the channel leading to the aortic valve was more direct and slightly larger, measuring  $3 \times 1.5$  cm., at the uppermost portion of the septum where these two channels joined. At the level of the defect, the septum varied from 6 to 8 mm. in thickness.

The aortic valve was situated more over the right than over the left ventricle. Its three cusps showed some variation in size, there being one large and two small cusps. The large cusp comprised about one-half the valvular surface, the remainder of the area being covered about equally by the two smaller cusps. At the level of the valve, the aorta measured 27 mm. in diameter.

The aortic arch was smooth and of normal size. There was no coarctation.

The coronary arteries were normal in size, and the walls were not thickened or sclerosed. The right coronary artery took its origin behind the large aortic cusp, and supplied practically the entire right ventricle. The left coronary artery branched normally and supplied the remainder of the heart.

*Pathological Diagnoses:* Congenital anomalies of the heart, (interventricular septal defect, pulmonary stenosis and regurgitation, dextroposition of the aorta, hypertrophy of the right ventricle), and bacterial (*Streptococcus viridans*) endocarditis of the tricuspid valve and of the pulmonary artery.

#### DISCUSSION

That subacute bacterial endocarditis complicating congenital cardiovascular disease was present in this case was evident after a brief clinical study, but the failure to make an exact diagnosis of the structural defects was due to several reasons. In the first place the great rarity of congenital pulmonary regurgitation made such a diagnosis improbable, the diastolic murmur being thought at first to be the result of secondary involvement of the pulmonary valve by the infection and later to be a part of the manifestation of patency of the ductus arteriosus even though unusual in timing (that is, the murmur was not continuous). The marked prominence of the pulmonary artery on x-ray examination was at the time attributed most readily to patency of the ductus arteriosus,



without the realization that long continued pulmonary regurgitation would be associated with pulmonary artery dilatation. The marked water-hammer pulse in the pulmonary artery as seen fluoroscopically was not given its correct significance as due to pulmonary regurgitation; patency of the ductus arteriosus does not produce so marked a pulmonary arterial pulsation as we found in this case. The second chief reason for our missing the exact diagnosis of structural defects in this case was the extraordinary paucity of evidence for the tetralogy of Fallot; the cyanosis was very slight, clubbing of the fingers was not apparent at all at first, and the blood showed a secondary anemia (due to the infection) rather than a polycythemia. Experience in this case should prove helpful in future cases.

#### SUMMARY

A very unusual case is reported of subacute bacterial (*Streptococcus viridans*) endocarditis and endarteritis involving the tricuspid valve and the pulmonary artery in a young woman twenty-one years old who showed the tetralogy of Fallot complicated by congenital pulmonary regurgitation.

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# POSTURAL HYPOTENSION WITH TACHYCARDIA. A CASE REPORT\*

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BRADBURY and Eggleston<sup>1</sup> in 1925 reported their observations of three patients whose blood pressures regularly fell below the critical level on standing in the erect position for a few minutes, and in their report they used the term "postural hypotension" to represent the particular condition described. Since 1925, several other cases of postural hypotension have been reported.<sup>2, 3, 4</sup> The marked features of the first reported cases were: critical fall of blood pressure with change from the horizontal to the upright position; slow pulse rate; incapacity to perspire; lowered basal metabolism; and signs of indefinite changes in the nervous system. Other features present in some, but not in all, of the reported cases were: chronic diarrhea; greater excretion of urine by night than by day; loss of sexual power; false appearance of youth, and secondary anemia.

In reviewing the reported cases of postural hypotension, it is observed that the essential and characteristic features common to all were: (1) the falling of the blood pressure below the critical level with the assumption of the upright position, and (2) the physical and psychical symptoms which were direct results of cerebral and cerebellar anemia. The other phenomena, not common to all the cases, were evidently individual or incidental.

Another case of marked postural hypotension is here presented. In this case tachycardia and abnormal changes in the electrocardiogram accompanied the fall in blood pressure with the change from the horizontal to the upright position.

## CASE REPORT

The patient, an electrician, thirty years of age, came under observation on November 30, 1931. He complained of marked dizziness, blurring of vision and faintness on sitting, standing or walking, sensations as of abnormal heart action, frequent nausea and distress in the upper abdomen, soreness of the lower abdomen, chronic diarrhea, and numbness and coldness of the hands and feet. He stated that all of these conditions had continued for several years and that for the past three years they had entirely incapacitated him from earning a livelihood.

The patient was kept under observation until December 29. The following notes are taken from the case records:

He states that he was a strong and healthy child and youth prior to entering the U. S. Army early in May, 1917, and that he had no sickness or injury of conse-

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queneo in the army service until about October 18, 1918, when he was "blown up" by a shell explosion, and, at the same time, was overcome by poison gas. He has no clear memory of what happened, and he thinks that he was unconscious for a short time. When he came to himself in a first aid station, he found that he had several slight and superficial wounds, that he had severe throat and lung irritation from the gas, and that he was very much upset nervously. He was returned to the United States as a "casual" and was continually under treatment in army hospitals until the following June. His weight early in 1918 had been 195 pounds. His weight in June, 1919, was 145 pounds. Since 1919 his weight has varied between 130 and 145 pounds.

From 1919 to 1928 he was greatly handicapped by dizziness and faintness when he was walking or standing, though he was able to hold a position for some years as resident operator of an electric power substation. He explains that in that position no strenuous exertion was required and that he was permitted to rest most of the time.

Since 1928 he has not been able to do any work. For this time he has not only been dizzy and faint when sitting, standing or walking, but he has also had much abdominal distress and an almost constant watery diarrhea. The abdominal distress has subsided and the stools have been formed only when he has rested in bed for several days. He has observed that his pulse has been slow while resting in bed, sometimes as slow as 40 per minute; but on rising from the bed his pulse has immediately become rapid. His wife has counted his pulse while standing and has reported that it is sometimes as fast as 160 per minute. He has often had "queer sensations" in his heart as though its action were irregular. When he has been walking, standing, or sitting for a time and has felt himself becoming dizzy and faint and his sight becoming blurred, he has learned to avoid serious injuries by immediately lying down or sitting down and bending forward with his head between his knees. On rising quickly from bed to a sitting position, he has often lost consciousness for a moment and has fallen to the floor and injured himself. Every time he has fallen he has regained consciousness on the instant that his head has become low.

He gives no history of having had rheumatic fever, chorea, scarlet fever, diphtheria, malaria, typhoid fever, pneumonia or tuberculosis. He has been subject to frequent chest pains, chronic cough, shortness of breath with exertion, and occasional mild asthmatic attacks since receiving the poison gas injuries in 1918. A few times he has raised slightly blood-streaked sputum, though he has never had a frank hemoptysis. He thinks that he perspires quite normally, and he has not observed that his general symptoms have been any more pronounced in the summer than in the winter. He has had no kidney or urinary trouble, to his knowledge. He has had no excessive thirst, and ordinarily he has had no nocturia. He habitually sleeps with a low pillow or with no pillow at all, and he has not been troubled with night dyspnea except occasional attacks of bronchial asthma. At various times he has observed that his feet and ankles have become swollen when walking, standing or sitting more than usual. For years his hands and feet have nearly always been cold and damp, and frequently his lower arm and leg become numb when he lies on one side.

His appetite is always poor. He has seldom vomited, though he is very frequently nauseated after eating. In recent years he has had much midepigastrie distress, especially after meals. He has found these troubles to be least annoying when his food has consisted chiefly of milk and when he has continued much of the time in bed. Alkaline powders give almost immediate temporary relief from the epigastrie distress, as does, also, the taking of milk during attacks. He has never been

jaundiced. He takes cream and other fats with no increase of the abdominal symptoms.

From 1918 to 1928 he was subject to attacks of diarrhea at intervals of a few months, and the attacks would usually last several weeks. For the past three years he has had two or three watery stools nearly every day. In recent years he has also had a lower abdominal distress and soreness, which he localizes as in the mid-area of the lower abdomen. He states that this distress has been constant rather than colicky and that it has been increased rather than decreased by the evacuation of the bowels. He had a left inguinal herniotomy in 1923 but has had no other abdominal operation.

He has never used much liquor, and none at all in recent years. He denies ever having used drugs, and there is nothing in his records or in his personal appearance that is suggestive of drug addiction. He smokes tobacco very moderately. He denies ever having had a venereal infection.

*Family History.*—The patient's father died of Rocky Mountain fever at sixty-five years of age. The mother is living and quite well at sixty-five years. He has had one brother and three sisters, and they are all living and well. He was married in 1926. His wife is well and has had two pregnancies by the marriage, each pregnancy resulting in a normal child, now living and well.

*Physical Examination.*—The patient is a very slender, poorly nourished and frail appearing white man, 73.5 inches tall and weighing 141.75 pounds, who has the appearance of his stated age of thirty-two years. He seems to be mentally alert; but he has a drawn and careworn expression of countenance. All his movements are slow and guarded. He has a very pronounced upper dorsal stoop, and he appears to be unable to stand erect, though he stands steadily with eyes closed. There are no notable tremors. The patellar reflexes are active.

His face and ears are very pale as he sits or stands, but their color becomes quite good almost immediately when he lies down. His hands and feet are moderately cyanotic when dependent, but they are of normal color when at the level of the body, and they retain their normal color after elevation for several minutes. His fingers are remarkably long and slender, and the finger nails are small, smooth and well shaped. His hands and feet are cold and damp. His skin is soft and quite free from lesions. There is an operative scar in the left inguinal area. No other gross scars of operation or injury are observed. There are no varicosities, and no definite edema is demonstrated.

His hair is thick, light brown, straight and rather coarse and oily. His face is symmetrical. He has no exophthalmos. The pupils are quite large. They are equal and regular, and they react to light, accommodation and convergence. The veins of the fundi are notably smaller when he is in the upright position than when he is in the horizontal position. The palpebral conjunctiva and the mucous membrane of the lips are very pale when he is upright. The thyroid gland is not palpable. The lateral cervical and the epitrochlear lymph nodes are just palpable. Other superficial lymph nodes are not remarkable.

*Summary of Further Observations.*—No definite evidences of disease were found in the upper respiratory tract, and the physical and roentgen-ray findings of the lungs were essentially negative. The roentgen-ray films showed total lack of calcification in the costal cartilages and a peculiar rarefaction of bone in the upper margins of the anterior ends of the third, fourth and fifth ribs on either side. The heart was shown to be rather small and centrally placed. A prominent, clearly outlined, oval shadow was observed in the position of the pulmonary artery. The significance of this shadow was not evident.

The visible and palpable cardiac impulses were slight, in the fifth interspace and eight centimeters from the midsternal line. No precordial thrills were palpable.

There was no abnormal precordial tenderness. The heart sounds were of normal character. Usually the rhythm was found to be regular, though at various times a rather marked sinus arrhythmia of the respiratory type was observed. A few times pulse irregularities were observed, the character of which was not definitely determined.

Most extraordinary changes in the pulse rate were produced simply by changing from the horizontal to the sitting position, and from the sitting position to the standing position. These changes in pulse rate were instant with the changes in position. The pulse rate regularly doubled with the change from lying down to standing, and this increase was approximately halved in the sitting position. This ratio of change in rate was fairly constant; when the pulse rate was 80 while lying in bed, it was found to be about 120 immediately when he sat up and 160 when he stood up; when the rate was 60 in bed, it was found to be approximately 120 when he rose to his feet. With the change from the upright to the horizontal position, the pulse rate was almost instantly halved.

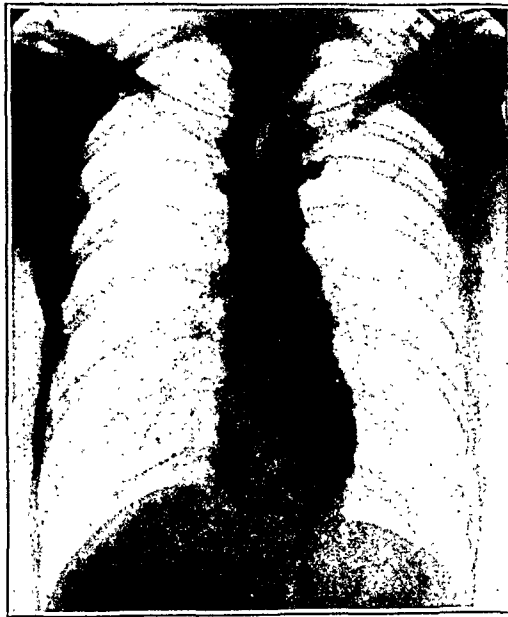


Fig. 1.

Even more remarkable than the variations of the pulse rate were the changes in the blood pressure readings with the changes in posture. With the patient lying down, the blood pressure readings were systolic 122 and diastolic 90 mm. With the patient sitting and with the sphygmomanometer cuff at approximately the level of his heart, the systolic reading was 115 and the diastolic 90 mm.; but when the arm was lifted so that the cuff was at approximately the level of his brain, the systolic reading was 80 and the diastolic 62 mm. With the patient standing and his arm at his side, the systolic reading was 90 and the diastolic 80 mm.; but when the arm was raised so that the cuff was at the level of his brain, the systolic pressure was 60 mm. and no definite diastolic reading could be made. Blood pressure readings in these various positions were repeated from time to time during the patient's stay in the hospital. The basic readings were variable, but, with the patient standing and with the cuff at the level of the brain, the systolic pressure was repeatedly read at 60 mm. On one occasion the systolic pressure at the brain level was read at 60 mm., and the patient was then required to stand, leaning against the wall, for ten minutes. The systolic reading at the brain level was then 50

mm. The patient asserted that he was not unusually faint, though his face and ears appeared to be quite bloodless.

The abdomen was long, flat and almost devoid of subcutaneous fat, but the musculature was fairly good, and there were no notable evidences of sagging of the abdominal viscera. No abnormalities could be palpated in the abdomen, though two areas of tenderness were located, one in the midepigastrium, the other midway between the umbilicus and the symphysis pubis. Firm supporting pressure on the lower abdomen, while the patient was in the upright position, caused him to complain bitterly of increased abdominal discomfort. His pulse continued weak and rapid while this pressure was applied, and some irregularity of the rhythm was noted, but the mechanism of the irregularity was not definitely determined.

Because of the report<sup>2</sup> of very satisfactory results in postural hypotension with the oral administration of ephedrine, it was hoped that similar results might be

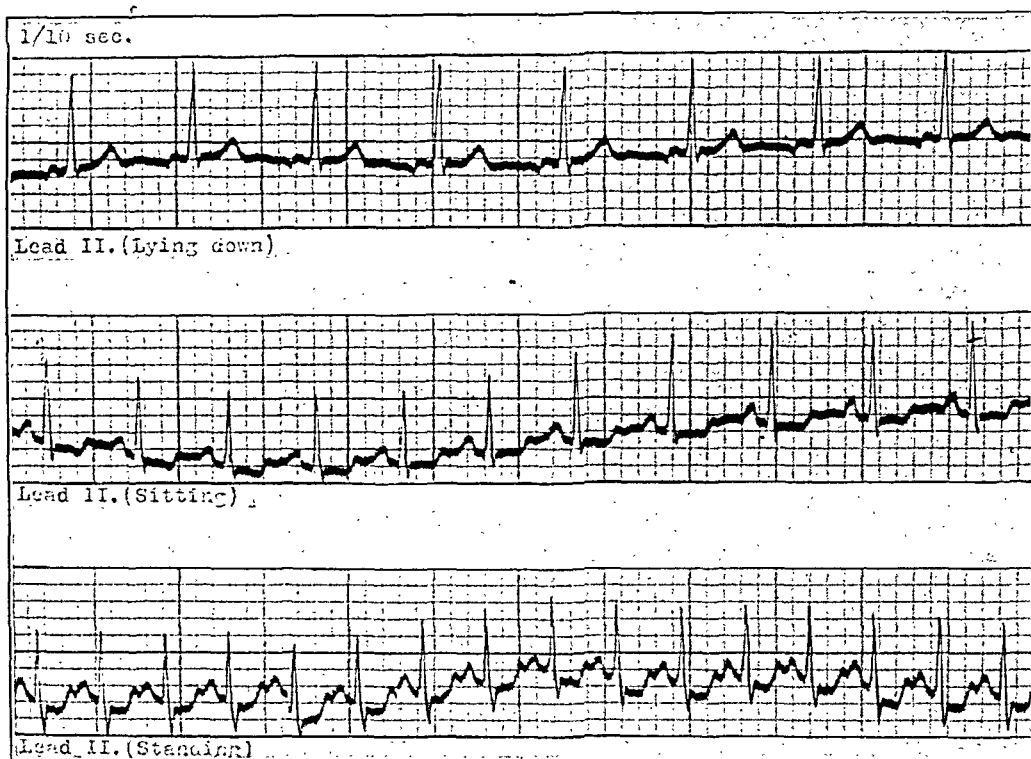


Fig. 2.—Case of postural hypotension.

obtained in this case. On December 19 the following notation was made on the patient's ward record: "At 12:45 P.M. the patient was given a  $\frac{3}{4}$  grain capsule of ephedrine sulphate, as a therapeutic test, in an attempt to raise his blood pressure. He complained of a chilly feeling shortly after taking the ephedrine. At 2:30 P.M. he reported that he had experienced a rather severe chill during the previous half hour, that his head had felt queer and that he had had sensations as of irregular heart action. However, he stated that those annoying symptoms were nearly passed. He was then lying quietly in bed and his pulse was quite regular and of good quality, at the rate of 60 per minute. He was asked to stand up by the bed. Immediately on standing, his pulse became very weak, its rate rose to 120 and his face became very pale. After standing for about a minute, he suddenly slumped to the floor. He no doubt would have injured himself had he been alone. Instantly, as his head became low, he recovered consciousness. After a few minutes

he was assisted to the sitting posture on the edge of the bed. Again his pulse became rapid and weak, and in a few moments he fell over in another faint. He recovered consciousness again immediately as his head went low, and almost instantly his pulse was slow and of good volume. These are the first times the patient has fainted since admission to the hospital. Further ephedrine medication is not deemed advisable."

*Laboratory Data.*—Blood: hemoglobin, 90 per cent; total red blood cells, 4,800,000 per c.mm.; total white cells, 7400; polymorphonuclears, 63 per cent; small mononuclears, 31 per cent; large mononuclears, 3 per cent; transitionals, 1 per cent; eosinophils, 1 per cent; basophils, 1 per cent. Red cells of normal appearance. Blood Wassermann reaction negative. Blood sugar: fasting, 125 mg.; one and a half hours after tolerance meal of 100 grams of glucose, 130 mg. Icterus index, 7. Van den Bergh tests: direct, negative; indirect, normal. Four basal metabolism estimates averaged -8.

Gastric analysis of test meal: Total acidity, 46; HCl 34; bile, +2; occult blood, +1; gastric mucus, +1. Eleven sputum reports were negative. Urinalysis reports were negative. Of 10 feces, 6 contained occult blood. No parasites or ova were found.

The report of the roentgen-ray examination of the gastrointestinal tract reads in part: "The stomach outlines readily and shows no defects. The duodenal bulb fills well. It shows a slight irregularity on its greater curvature near its apex. This is not constant and is of doubtful significance." The stomach was of the fish-hook type. The transverse colon was near the level of the iliac crests. The films at six hours, twenty-four hours and forty-eight hours revealed no definite abnormalities.

#### COMMENT

The three electrocardiograms here presented were taken within a few minutes. The first was taken with the patient lying in bed. For the second, he was asked to sit upon the side of the bed, the electrodes being still attached to his wrists and ankle. After about a half minute, the time required for the beam of light to become adjusted, the second record was taken. Then the patient was required to stand by the bedside while the third record was taken. The order of procedure was then reversed, and electrocardiograms were taken immediately on sitting down and on lying down. Only one of the two series is here presented, as they were found to be identical.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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McMillan, Thomas M., and Bellet, Samuel: Auricular Flutter: Some of Its Clinical Manifestations and Its Treatment Based on a Study of 65 Cases. *Am. J. M. Sc.* 184: 33, 1932.

A series of 65 cases of auricular flutter is reported, 12 of which were classed as paroxysmal and 43 as established flutter. Seven were due to drugs and 3 received no treatment and were therefore unclassified. The effects of digitalis upon the auricular rate are discussed. It is believed that the results of treatment of the disturbance were quite successful. Of the entire 65 cases a return to normal rhythm was secured in 66.1 per cent. Considering only the cases of established flutter, normal rhythm was successfully restored in 74.4 per cent of the cases.

The method of choice in this series of cases was the use of digitalis until fibrillation was established. Digitalis was then discontinued and unless a normal rhythm had spontaneously returned within a week, the administration of quinidin was begun. The latter drug was used alone after digitalis had either failed to bring on fibrillation or had brought on certain toxic manifestations which rendered a further use of digitalis inadvisable.

Landis, Eugene M., Jonas, L., Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion. *J. Clin. Invest.* 11: 717, 1932.

It was the purpose of these studies to measure the effect of graded venous congestion on the movement of fluid from the blood to the tissue spaces. Blood samples removed from the arm veins were compared in order to measure the filtration of fluid resulting from the increased venous pressure. The loss of protein through the capillary wall was estimated at venous pressures of 80, 60 and 40 mm. Hg. Comparison of hemoglobin readings and red cell counts showed that during venous congestion the fluid is lost chiefly from the plasma. The loss of fluid could be detected at venous pressures as low as 20 mm. Hg and amounted to between 0.0 and 2.3 c.c. per 100 c.c. of blood. The amount of fluid lost from the blood was conspicuously greater at higher venous pressures; venous congestion of 80 mm. Hg filtered as much as 19.5 c.c. per 100 c.c. of blood.

At a venous pressure of 80 mm. Hg protein was lost from the blood plasma in an amount indicating that the capillary filtrate contained an average of 1.5 per cent of protein. At a venous pressure of 60 mm. Hg very little protein loss could be detected and the capillary filtrate contained an average of 0.3 per cent protein.

Two cases of edema are described in which fluid was collected during venous congestion. The protein content of the edema fluid was 0.39 and 0.09 per cent, indicating that the capillary wall retained approximately 95 per cent of the plasma protein.

Dameshek, William, and Loman, Julius: Direct Intra-Arterial Blood Pressure Readings in Man. *Am. J. Physiol.* 101: 140, 1932.

The intra-arterial pressure in about 50 individuals was determined by a direct method which was compared with the usual indirect ones. This direct method con-



sisted of introducing a 20-gauge needle into the artery, usually the brachial, and connecting it through a 3-way stopcock with a syringe and an aneroid sphygmomanometer. The method used was subjected to a large series of experiments to determine its reliability. It was finally determined that the greater the pulse pressure the less accurate was the technic used, that a mean rather than a systolic pressure was determined.

The pressure within the common carotid, femoral and brachial arteries was compared in eight cases. The brachial artery pressure was slightly higher than that of either the carotid or femoral arteries. The apparent discrepancy between indirect and direct blood pressure readings in arteriosclerosis was concluded to be due to the high pulse pressure which is present in that condition. The indirect method of sphygmomanometry appears to be accurate even in the presence of marked arteriosclerosis.

**Reid, William D., and Levene, George: Roentgenologic Consideration of Mitral Heart Disease. *New Eng. J. Med.* 206: 1026, 1932.**

While early mitral disease is often difficult of recognition clinically, it frequently may be identified by careful roentgen examination. The authors have recently described a method of recording the various measurements of the heart and have stated that the ratio that exists between the size of the auricles and ventricles may be of importance in diagnosis. In mitral stenosis an altered relationship of auricular and ventricular areas is a typical and diagnostic roentgenographic sign. They believe that the high index of this ratio is the most important single factor in the early roentgenographic identification of this condition. Mitral insufficiency can be demonstrated by roentgen examination and the organic and functional forms differentiated.

*Roentgen examination affords accurate information concerning the course of mitral disease under treatment.*

**Lichtman, S. S., and Gross, Louis: Streptococci in the Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases. *Arch. Int. Med.* 49: 1078, 1932.**

A study of 5,233 consecutive blood cultures in a general hospital shows that with adequately sensitive methods an incidence of nonhemolytic streptococcemia between 4 and 15.5 per cent with an average of 6 per cent occurs in at least nine diseases. That is, acute rheumatic fever with polyarthritis, chronic rheumatic cardiovalvular disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, leucemia, colitis, meningococcus meningitis and pyelitis and pyelonephritis. On the basis of the incidence of the "transient" streptococcemia alone, these organisms cannot justifiably be considered as the causative agents of these diseases.

**Styron, Norma C., and Spicer, Sophie: Dissociation of Streptococcus Cardio-Arthritidis. *J. Infect. Dis.* 50: 490, 1932.**

The work on microbial dissociation reported in this paper has been done with the R 1 and R 9 strains of *S. cardio-arthritis* isolated by Small from blood cultures of patients with rheumatic fever. Fifty cubic centimeter volumes of phosphate broth with or without dextrose, enriched with 2, 5 and 10 per cent concentrations of peptone support dissociation. The percentage of peptone most favorable to the process is 5. Strain R 9 was much more unstable than strain R 1. As a result of dissociation, two culture types have been obtained for each strain. As far as tested, no qualitative difference in carbohydrate fermentation, in action on milk and in production of indol has been demonstrated. No tendency to form methemoglobin was evidenced in any of the types.

Intradermal skin tests in rabbits to test the allergic capacity of the two types

resulted in lesions having distinct characters. The antigenic relationship of the two strains have also been investigated. It was found that cultivation in fluid mediums readily caused one of the strains, R 9 to show a reversion of the atypical forms to the more typical ones. A partial change from typical to atypical in the same strain was sometimes accomplished but it was very infrequent.

**Dikar, Lewis: Acute Bacterial Endocarditis Due to Bacterium Acidi-Lactici.** Arch. Int. Med. 49: 788, 1932.

Two cases of *Bacterium acidi-lactici* endocarditis closely resembling cases of *Bacterium coli* are reported because of their rarity. It is believed that more complete bacteriologic studies of cases of *Bacterium coli* sepsis will undoubtedly bring to light more examples of *Bacterium acidi-lactici* infections. The coincidence of aortic valve involvement in two cases of *Bacterium acidi-lactici* endocarditis and in two cases of *Bacterium coli* endocarditis is pointed out.

**Don, C. S. D., Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block With Varying Ventricular Complexes.** Heart 16: 145, 1932.

A case of complete heart block is described in which the ventricular complexes vary in form. Pathological examination showed that the bifurcation of the A-V bundle was destroyed by disease; the main bundle was separated from its branches and the right branch from the left. It is pointed out that these findings are similar to the results of experiments on dogs carried out by Wilson and Herrman in which both bundle branches were cut. Electrocardiograms from this patient are like those of the dogs and show changes in the ventricular complexes which can be interpreted as due to a shifting of the pacemaker from one ventricle to the other with transitional forms showing that two pacemakers were competing for the ventricular rhythm. The intravenous injection of atropin temporarily abolished the variation in the ventricular complexes which assumed an intermediate form.

**Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block Due to an Arterial Angioma.** Heart 16: 137, 1932.

A case is described of complete heart block developing in an adult and due to destruction of the terminal portion and bifurcation of the A-V bundle by an arterial angioma. At autopsy the examination of the heart revealed an angioma similar to those which may be found elsewhere in the body. A clinical history in the present case indicated the growth of the tumor during the last few years of life so as to involve the conducting system of the heart.

**Gil, Urbano Gonzalez: The T Wave of the Electrocardiogram. Its Pathological Interpretation and Prognostic Value.** Arch. de Cardio. Y. Hemato. 13: 187, 1932.

The author has attempted to decide in the present work the importance of the different causes which give place to an inversion of the T-wave in order to judge the prognostic value of this electrocardiographic alteration. At the same time, it is interesting to know the precise difference between the pure inversions of this wave and those which are accompanied by other modifications in the electrical tracing where the prognostic signification is very distinct. Finally, the author takes into consideration the unstable character of this inversion which it is necessary to recognize if one does not wish to make an erroneous prognosis.

**Prodger, S. H., and Dennig, H.: A Study of the Circulation in Obesity.** J. Clin. Invest. 11: 789, 1932.

Various phases of the circulation were studied in a group of obese patients who had no demonstrable pathological changes in the circulatory system, chiefly in their

response to mild exercise in the form of walking on a tread mill. The results were compared with the results in a group of normal people. The responses of the cardiac output and arteriovenous oxygen differences to exercise were similar in the two groups. The chief differences between the two groups were found in the vital capacities and in the pulse rates, respiratory rates, blood lactic acid changes, oxygen consumption and oxygen debts in exercise.

On the basis of the findings presented, it is believed that the symptoms which are so commonly associated with cardiac insufficiency and which are frequently observed in cases of simple obesity are not due to an inefficient circulatory response but rather to mechanical and chemical disturbances associated with obesity.

**Andrus, E. Cowles, and McEachern, Donald: The Cardiac Manifestations of Hyperthyroidism. Am. J. Med. Sc. 183: 741, 1932.**

In this brief résumé, the authors point out the present conception of the effects of hyperthyroidism upon the heart. They believe that this effect is from its own accelerated metabolism and from the load thrown upon it by the metabolism of the body as a whole.

From the experimental work done on animals, it is believed that the auricles from thyrotoxic animals were more dependent than were the normal controls upon their contemporary oxygen supply which in turn suggested that their rate of oxygen consumption might be increased beyond the normal. It also seemed possible that these preparations were either elaborating lactic acid at the faster rate or were less able to oxidize it or get rid of it by diffusion than the normal auricles. Direct chemical estimations of the lactic acid in cardiac muscle was found to be almost double in the thyrotoxic group as compared with normal rabbits. The glucose and total base was found to have undergone no significant change.

**Richards, Dickinson W., Riley, Constance B., and Hiscock, Mabelle: Cardiac Output Following Artificial Pneumothorax in Man. Arch. Int. Med. 49: 994, 1932.**

Studies of the cardiac output and other functions of the circulation have been made before and after artificial pneumothorax in three cases of pulmonary tuberculosis. The cardiac output was decreased following pneumothorax in all cases. Among the other changes that occurred were: decreased vital capacity and residual air and lowered alveolar and blood carbon dioxide levels. The interrelations of some of these changes are discussed.

**Bennet, Dudley W., and Kerr, William J.: A Note on Auricular Sounds in a Case of Auricular Flutter. Heart 16: 109, 1932.**

In a patient presenting a disturbed cardiac rhythm resulting from auricular flutter with irregular block, low pitched sound in addition to the usual first and second heart sounds was heard through a binaural stethoscope. The rhythm of the extra sound was regular and rapid, probably about 300 per minute; it was audible at various points over the precordium and most clearly at the third left interspace close to the sternum. The ventricular rhythm was irregular, its average rate being 120 per minute; the first sound was muffled and indistinct while the second was loud and rough. Digital pressure over the left carotid sheath temporarily brought the ventricles to a stand still, the first and second sounds disappearing. During cessation of ventricular contraction the rapid faint ticking sound was still heard, produced apparently by contraction of the auricles.

This interpretation of the adventitious sound was confirmed by recording the electrocardiogram through one of the strings of a double stringed Einthoven galvanometer. The heart sounds were recorded through a sensitive microphone placed on the precordium and electrically connected to a Western Electric stethoscope. The

outgoing wires of the stethoscope were connected to the second string of the Einthoven galvanometer. Records obtained from this procedure are published. From the examination of these records made while ventricular flutter was present and while ventricular action was stopped by vagal pressure, it seems that the sound heard was associated with auricular contraction.

**Reid, William D.: The Causation and Propagation of the Heart Beat.** New Eng. J. Med. 206: 1254, 1932.

Data selected from the literature of biochemistry and physiology which form a reasonable explanation of the origin of the heart beat are briefly presented. The author proceeds to discuss these data and emphasizes the lowering of the electrical potential of the heart cells due mainly to the action of potassium ions brought by the blood to the heart.

He discusses the various hypotheses which have been offered to explain the origin of the heart beat in the sinus node rather than in other areas of the heart. This paper presents an interesting short review of these facts as they are known today.

**Lewis, Sir Thomas: Raynaud's Disease.** New Eng. J. Med. 206: 1192, 1932.

The author presented a brief summary of his theory as to the mechanism of Raynaud's disease at the meeting of the New England Heart Association. He gave a general idea of experimental work done to support his views. He believes that the well known phenomena associated with this condition are not due to any dysfunction of the vasomotor system but to a "local fault," probably in the arteries of the digits involved. The present article is made out of essential abstracts from an original article published in *Heart*, volume 15, page 7, 1929.

**White, James C.: Raynaud's Disease.** New Eng. J. Med. 206: 1194, 1932.

Six cases of typical Raynaud's disease are reported with observations on the immediate and late effects of sympathetic neurectomy.

Resection of the two upper dorsal ganglia or of the second to fourth lumbar ganglia brought about an immediate paralysis of sympathetic tonus in each case. Whereas, vasomotor paralysis following lumbar sympathectomy has been permanent, the dorsal operation has been followed by a recurrence of sympathetic nerve function in two out of the five cases reported here and of five more not included in this group. Sympathetic nerve activity has reappeared at the end of six months accompanied by the color changes, pain, coldness and ulceration in the tips of the fingers characteristic of Raynaud's disease. When the regenerated vasoconstrictor fibres were again adequately blocked by novocaine or by reoperation, there was a second disappearance of the manifestations of the disease. Therefore, resection of the first and second dorsal sympathetic ganglia alone is insufficient to cause a permanent vasomotor paralysis of the arm. In the recent cases where the operation has been extended upward to include the inferior cervical ganglion, it is hoped that the results will be as permanent as those in the lower extremity.

Advanced stages of the disease with long standing ulceration and sclerodermatous changes may fail to recover completely after vasomotor paralysis. These instances are satisfactorily explained by Lewis' theory of local pathology in the digital vessels.

From the theoretical standpoint, early uncomplicated cases of the disease may be explained either on the basis of Raynaud's original conception of a vasomotor neurosis or by Lewis' theory that normal vasoconstrictor impulses cause the attacks of partial asphyxia by acting on abnormal digital arterioles. Certain objections have been pointed out against each hypothesis. It is, therefore, essential to reserve final judgment until the evidence of one or the other becomes unequivocal.

**Levine, Harold D.: Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation.** Arch. Int. Med. 49: 808, 1932.

In a series of thirty-six experiments performed on cats, it was found that quinidine sulphate definitely inhibited the facility with which ventricular fibrillation could be produced by cardiac stimulation. It was also found that this effect could not be attributed to manipulation of the heart and the resulting fatigue of the muscle or to the time consumed in the experiments. It is suggested that these results offer a rational background for proper quinidine therapy as a method of preventing sudden death in those conditions in which ventricular fibrillation is prone to occur.

**Weisman, S. A.: Auricular Fibrillation. Ambulatory Treatment With Quinidine.** Arch. Int. Med. 49: 728, 1932.

Twenty-four cases of auricular fibrillation who were treated satisfactorily with quinidine by the ambulatory method are reported. Normal rhythm was restored in 17 of these cases.

Of the successfully treated patients, 4 had rheumatic valvular disease, 10 had hypertension, 1 had coronary sclerosis, 1 had diabetes and hypertension, 1 had syphilitic aortitis and 1 had an apparently normal heart. Eighteen of the 24 patients were fifty years of age or over; in 14 of this group, the heart was restored to regular rhythm; in 3 of the remaining 6 patients, regular rhythm was restored. Chronic fibrillation from two months to ten or twelve years had existed in all but one case. Small doses of quinidine were given to start with, following a brief period of the use of tincture of digitalis.

**Hyman, Harold T., and Fenichel, Nathan M.: The Management of the Decompensated Cardiac Invalid.** Am. J. M. Sc. 183: 748, 1932.

The records of 100 decompensated cardiac invalids have been summarized and the therapeutic regimen noted. The patients in most instances were victims of rheumatic fever who no longer presented any evidence of activity of heart infection. In the arteriosclerotic group, the acute episodes, such as thrombosis and embolism were part of the past history. The problem was sharply limited to the management of the advanced and decompensated cardiac invalid who had already passed through the active stages of the illness and who had failed to respond to home or ambulatory treatment.

Eight patients were restored to compensation by physiologic rest and dietotherapy. Mechanical removal of fluid from the serous cavities was practiced in 14 of the group. Fifty-six patients were specifically benefited by digitalis and all but 4 in this group had auricular fibrillation.

Sixty-four patients, edematous despite physiologic rest, dietotherapy and digitalization, were relieved by the administration of salyrgan with or without the simultaneous administration of urea and the acid salts. Five patients responded by diuresis to urea alone.

The four cardinal steps in the management of the decompensated cardiac invalid are: (1) physiologic rest and dietotherapy; (2) mechanical evacuation of fluid from the serous cavities; (3) digitalization and (4) the use of diuretics. These four forms of management are discussed.

**Hyman, Harold T., and Fenichel, Nathan M.: The Management of the Decompensated Cardiac Invalid. II. Effects of Specific Medication.** Am. J. M. Sc. 183: 753, 1932.

Drug therapy is indicated in the cardiac invalid who remains decompensated despite physiologic rest, dietotherapy and the mechanical evacuation of fluid from

the serous cavities. Digitalis is invaluable in those patients who present auricular fibrillation. Diuretics are equal in importance to digitalis in the management of the decompensated cardiac invalid. Their use is independent of the cardiac rhythm.

Moore, Joseph Earle, Danglade, James H., and Reisinger, John C.: **Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm. Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients.** *Arch. Int. Med.* 49: 753, 1932.

In the twenty year period from 1910 to 1930, there came to necropsy in the Johns Hopkins Hospital, 105 patients with uncomplicated syphilitic aortitis. The clinical diagnosis of syphilitic aortitis was correctly made during life in 4 of the 105 patients; in 13 more it was suspected that something was wrong with the aorta. On the basis of the symptoms and physical signs recorded, the diagnosis might have been correctly made in 35 additional patients. In 12 instances, the diagnosis was obscured by some other form of cardiovascular disease. Thirty-four patients died with hearts and aortas thought clinically to be normal.

Syphilis was infrequently a major feature of the fatal illness; when it was, aortitis was more often diagnosed correctly than when the final illness was unrelated to syphilis. Hypertension was an infrequent accompaniment of syphilitic aortitis and in spite of the confusion it created in the individual case, its presence did not prevent correct diagnoses. The Wassermann reaction of the blood was positive in 75 per cent of these cases.

The success or failure of the clinical diagnosis is compared with the extent of pathologic change present in the aorta. Symptoms and signs permitting a diagnosis were present in about half of those who showed only relatively slight gross pathologic changes. The criteria of diagnosis are discussed and seven frequently found symptoms or signs listed. The most important are roentgenologic evidence of aortic inhibition, increased retromanubrial dullness, a history of circulatory embarrassment, a change in the tonal quality of aortic second sounds. The other signs less frequently observed are progressive cardiac failure, substernal pain and paroxysmal dyspnea. In patients with proved late syphilis the presence of any three of the seven criteria listed is considered justification for the diagnosis of uncomplicated syphilitic aortitis.

Moore, Joseph Earle, Danglade, James H., and Reisinger, John C.: **Treatment of Cardiovascular Syphilis. Results Obtained in Fifty-Three Patients With Aortic Aneurysm and in One Hundred and Twelve With Aortic Regurgitation.** *Arch. Int. Med.* 49: 879, 1932.

A general consideration of the subject of treatment of cardiovascular syphilis is presented. The material permits some conclusions bearing on important questions of the incidence of cardiovascular syphilis.

An earlier study of the outcome of treatment in early syphilis in the clinic revealed that cardiovascular syphilis developed among these treated patients in inverse ratio to the amount of treatment given early in the infection. Not one of the 117 patients with early syphilis who received three or more courses of arsphenamine and treatment with mercury during periods between the courses, presented any evidence of cardiovascular involvement during the period of observation, while 24 of the 285 patients who had received less than this amount of treatment were observed to acquire syphilitic aortitis, aneurysm or aortic regurgitation. Adequate treatment for early syphilis almost certainly protects the majority of patients so treated against subsequent cardiovascular syphilis.

One hundred and forty-seven of the patients had never received any treatment

for syphilis before the development of cardiovascular syphilis; of the remainder not one had received adequate treatment for early syphilis. Only 4 of the 165 had received arsphenamine at the time of early syphilis and none of these got more than three injections. The evolution of the method of treatment now in use by the authors and subject to minor modifications by many other investigators is outlined. Special stress is laid on sudden death during or immediately following the administration of arsphenamine to patients with syphilitic heart disease, presumably due to ventricular fibrillation; on sudden death from twenty-four to forty-eight hours following an injection due to therapeutic shock and on the therapeutic paradox. The measures taken to avoid these reactions have resulted in the adoption of a method of treatment which is described in detail. This method includes adequate general medical care and the cautious use of mercury, bismuth, the iodides, neoarsphenamine and bismarsen in small doses. All reactions to treatment are meticulously avoided and treatment is prolonged over a period of years.

Using this method of treatment and subdividing the material into four groups on the basis of the amount of treatment given, it is shown that in 22 patients with aortic aneurysm, who received little or no treatment, the mortality during the period of observation was 90 per cent and that the average duration of life from the onset of symptoms to death or, in living patients, to the last observation was nineteen months. In 15 well treated patients with aortic aneurysm the mortality was 40 per cent and the average duration of life seventy-five months. The mortality in 57 patients with aortic regurgitation who received little or no treatment was 91 per cent and the average duration of life thirty months. In 25 well treated patients, the mortality was 16 per cent and the average duration of life seventy-one months. So far as can be judged from the average duration of symptoms, the respective numbers of patients symptom free before and after treatment and the incidence of congestive heart failure before and after treatment in the various treatment groups, the patients in the various groups were approximately similar. That is, it does not appear that the reported deaths occurred only among patients desperately ill before treatment and the reported success only among patients with less serious or less rapidly progressive lesions.

The occurrence of congestive heart failure before or after treatment is of serious prognostic import. In this connection the material is analyzed from several standpoints. Twenty-one of the surviving 56 patients of this series are symptom free and able to work; 26 have some persistent symptoms but can carry on at light work; 9 are incapacitated. Twenty-eight of the 47 still able to work were well treated for syphilis.

Symptomatic relief in cardiovascular syphilis is frequently obtained and its probability is in direct proportion to the amount of treatment given. The occasional alteration of physical signs during or after treatment is discussed. In an analysis from the standpoint of ability to work before and after treatment, well treated patients show up much more favorably than those untreated or badly treated.

Fifty-seven of the 165 patients died of progressive cardiac failure; 28 died suddenly; 11 are dead but the cause of death is unknown; 13 died of some other than cardiovascular syphilis.

The arsenical drugs given to these patients are tabulated and the reactions to them analyzed. From these data the authors conclude that the arsenical drugs of choice are, neoarsphenamine, bismarsen and silver arsphenamine. Old arsphenamine should not be employed in patients with aneurysm or aortic regurgitation. The use of tryparsamide should be limited to patients with complicating neurosyphilis. A fixed positive Wassermann reaction of the blood is the rule in cardiovascular syphilis and the response of this reaction to treatment may be completely disregarded.

Nuzum, Franklin R., and Elliot, Albert H.: Pancreatic Extract in the Treatment of Angina Pectoris and Intermittent Claudication. *Arch. Int. Med.* 49: 1007, 1932.

An insulin free extract of the pancreas, a vasodilator that modifies the pressor effects of epinephrine and dilates the coronary arteries of the rabbit's heart to a degree exceeding that produced by drugs of the purine group was administered intramuscularly to 20 patients with angina pectoris. Two were not helped, 5 were somewhat relieved, 11 were greatly helped and 2 who were benefited by treatment died later. Forty-one patients with angina pectoris who received the usual treatment and were followed for a like period of time were studied as a control series. In 10 instances no benefit was observed, 14 experienced moderate relief, 14 received pronounced benefit and 3 died. Five patients with intermittent claudication, one with thromboangiitis obliterans and one with cerebral vascular spasms and angina pectoris were benefited to a pronounced degree by treatment with the extract.

Goldring, William, and Chasis, Herbert: Thiocyanate Therapy in Hypertension: II. Its Effect on Blood Pressure. *Arch. Int. Med.* 49: 934, 1932.

Data are presented on 50 patients subjected to 74 trials with thiocyanate therapy. In 46 of these patients the hypertension was of essential type and in the remaining 4 patients it was associated with chronic diffuse glomerulonephritis. Forty-four trials were made in the outpatient clinic and thirty with the patients confined to the hospital.

Observations were made on the daily excretion rate of thiocyanate in the urine and the number of days necessary for its complete elimination after continuous medication and after a single dose in patients with essential hypertension and nephritic hypertension and in normal persons. Toxic effects of thiocyanate were not observed in 4 patients with chronic diffuse glomerulonephritis, 3 of whom responded by a satisfactory fall in blood pressure. Therapeutic, toxic or fatal effects could not be anticipated from the amount of the drug administered. The dosage found to be most effective in lowering blood pressure and least often attended by toxic manifestations was 0.326 grams given daily over a period of from fourteen to seventy-eight days. Thiocyanate was 31 per cent effective in lowering blood pressure in this series. Toxic manifestations occurred in 13 patients or 17 per cent of the total group studied.

Miller, H. R., and Feldman, A.: Prolonged Use of Massive Doses of Urea in Cardiac Dropsy. *Arch. Int. Med.* 49: 964, 1932.

Urea administered in the way described has been found to be an effective diuretic over long periods of time in selected cases. Whereas, it can function alone over many months in keeping the patient edema free, it may require the supplemental use of other diuretics. This is true for the patient with or without auricular fibrillation. Cases are reported in which its unbroken administration continued over three years. Once the signs of congestive heart failure have been removed urea is valuable in preventing their recurrence. The drug tends to maintain the patients' weight at a low and constant edema free level over months and even years. During such periods the patients often required little or no restrictions of the intake of fluid or salt within ordinary dietary limits.



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